Ketamine: An Update for Obstetric Anesthesia

Yuying Tang[1], Renyu Liu[2] and Peishan Zhao[3]*

[1]*Department of Anesthesiology, West China Second Hospital, Sichuan University, Chengdu, China*

[2]*Department of Anesthesiology and Critical Care, Hospital of the University of Pennsylvania, Pennsylvania, USA*

[3]*Department of Anesthesiology, Tufts Medical Center, Tufts University School of Medicine, Boston, USA*

Abstract

Ketamine was widely used in obstetric anesthesia soon after its invention. It was gradually less considered, if not forgotten, by medical community with the appearance of new general anaesthetics and more effective neuraxial analgesia. Research in the last 2 decades has reanimated ketamine as a potent analgesic and possible antidepressant. In this review, we will briefly summarize obstetric relevant pharmacology of ketamine; present the previous clinical experiences with ketamine in parturient; and discuss some controversies on its clinical application in obstetric anesthesia and possible future research.

Keywords

Ketamine, Obstetrics, Anesthesia

Introduction

The history of ketamine can be traced back to 1962 when a Phencyclidine (PCP) derivative CI-581 (2-(O-chlorophenyl)-2-(methylamino) cyclohexanone) called R (-) ketamine was synthesized by Stevens [1]. The first human experiment of R (-) ketamine in volunteers was performed in 1964 [2], and then it was first safely used in childbirth in 1966 [3]. In 1970, FDA approved ketamine as a clinical anesthetic in adults [4]. Despite unpleasant psychodysleptic effects of ketamine, its unique advantages, including rapid onset, potent analgesia and favorable cardiopulmanory profiles made it a popular anesthetic agent shortly after it was invented. Ketamine used to be widely used in Obstetric (OB) anesthesia, either as a sole anesthetic agent or combined with inhalational anesthetics in Vaginal Delivery (VD) and Cesarean Delivery (CD) in 1970s [5]. However, with the widespread acceptance of safer and more effective neuraxial analgesia/anesthesia and application of new intravenous (i.v.) anesthetics, such as propofol, the use of ketamine in OB anesthesia was out of favor in 1980s and early 1990s due to its side effects, such as unpleasant hallucination, nightmare and nausea [6-8].

In the last twenty years, research on ketamine produced many new evidences that either challenge the traditional concepts or present new information. For example, ketamine is now frequently used for perioperative pain management instead of as an induction agent of General Anesthesia (GA) [9,10]. Meanwhile, use of ketamine in OB patients has revived as a rescue analgesic for inadequate neuraxial anesthesia during CD. Studies have also shown that preemptive analgesia with i.v. ketamine improved post-operative pain control after CD [11-13]. The potential neuroprotection and neurotoxicity of ketamine on fetus and newborn remain elusive [14-17]. Several early reviews addressed the pharmacological characteristics and clinical experiences with ketamine [6,18,19]. Gorssen specifically reviewed ketamine use in OB anesthesia before mid 1970s [5]. Recently, a thorough review of ketamine pharmacology and pain management has been published [20]. Furthermore, its high potential for abuse has been discussed intensively among Chinese and American physicians [21]. The aim of this article is to briefly review relevant pharmacology of ketamine and its benefit and risk for parturient and neonate, to summarize previous clinical experiences with ketamine in OB patient, and to discuss some controversies on ketamine use in OB anesthesia and possible future research.

Methods

Relevant articles in the PubMed Medline database were searched using the key words ''ketamine'', ''obstetric anesthesia'', "labor and delivery", "Cesarean delivery" ''cesarean section'' and ''parturient''. Our search was limited to English-language studies. Some publications were identified from review articles. The last search was on May 30, 2017.

Pharmacological Mechanisms of Ketamine

Molecular mechanisms of ketamine

Ketamine is a noncompetitive antagonist of the N-Methyl-D-aspartate (NMDA) receptor [22]. It inactivates NMDA receptor by binding to its intrachannel PCP site and thus prevents a massive influx of calcium (Ca^{2+}) and membrane depolarization [23]. Low concentrations of ketamine predominantly block closed ion channels, whereas at higher concentrations ketamine blocks both open and closed ion channels of NMDA receptor [23]. Blockade of NMDA receptors in neurons that distributed along the

thalamo-cortical pathway, the biological basis of human consciousness, produces functional dissociation between thalamo-cortical and limbic systems, and a status of dissociative anesthesia that is while the patient is unaware of surrounding environment by losing the perception of visual, auditory, proprioceptive, and painful stimuli, he can still move and breathe spontaneously [22].

Analgesic effect of ketamine

Another distinctive feature of ketamine is its potent analgesic effect produced at subanesthetic concentrations or low doses [24]. The low dose ketamine is defined as a bolus dose of < 2 mg/ kg when given intramuscularly (i.m.) or < 1 mg/kg when administered via i.v. or epidural route. For continuous i.v. infusion, low dose ketamine is defined as a rate ≤ 20 µg/kg/min [24,25]. Previous studies have indicated that ketamine plasma concentrations at 0.15 µg/ml and 0.04 µg/ml following 0.5 mg/Kg of i.m. or oral administration produced significant analgesic effect. These concenterations were much lower than awakening plasma concentrations of 0.64 -1.12 µg/ml [26]. Except for preventing Ca^{2+} influx, ketamine also decreases the channel opening time, the frequency of channel opening and the amplification of the response to repeated stimulation, a phenomenon called "wind up". Therefore, subanesthetic dose of ketamine is currently not only used for acute pain management, but also recommended as an adjuvant to local anesthetics and opioids in a multimodal therapy of chronic pain to prevent allodynia and hyperalgesia [27].

Ketamine analgesia is mainly mediated by noncompetitive blockade of the NMDA receptors in the Central Nervous System (CNS). Although several other receptors, including monoaminergic (noradrenaline and serotonin) receptors [28] and nicotinic acetylcholine receptors [29] were claimed to be involved in the analgesic mechanisms of ketamine as well, the affinities of ketamine with those receptors were significantly less than that with the NMDA receptors [19]. Animal study showed µ- and δ-opioid receptors were related to ketamine analgesia [30]. However, ketamine analgesia did not seem to be the result from interaction with opioid recptors in humans since its analgesic effect is not completely antagonized by naloxone [31].

Ketamine analgesia is also explained by its anti-inflammatory effects. Decreased tumour necrosis factor α (TNF-α), Interleukin 6 (IL-6), and IL-8 levels as well as stabilization of neutrophil activation and suppressed NF-κB expression have been observed in animal models and in patients receiving ketamine [32-35].

Functional Magnetic Resonance Imaging (fMRI) has shown that decreased pain perception with ketamine was associated with a dose-dependent reduction of pain-induced cerebral activities [36]. In addition to supraspinal actions, blockade of afferent signals from the spino-reticular pathways is also important in ketamine analgesia [37].

The pharmacodynamic effects of ketamine on the cardiovascular system of parturients

Ketamine preserves vascular resistance and systemic arterial Blood Pressure (BP) by increasing release and inhibiting reuptake of catecholamines in circulation and the CNS [38]. The favorable cardiovascular effect of ketamine makes it an optimal anesthetic agent in hypotensive patients.

An augmented Pulmonary Arterial Pressure (PAP) has been observed after 2 mg/kg of ketamine i.v. injection in patients undergoing diagnostic cardiac catheterization [38]. However, instead of a direct effect of ketamine, increased PAP may be related to elevated partial pressure of carbon dioxide and declined arterial oxygen in inadequately spontaneous breathing patients [38]. In fact, at clinically relevant doses ketamine causes significant dose-dependent pulmonary vasodilatation which is partly mediated by activation of L-type calcium channels [39,40].

The pharmacodynamic effects of ketamine on respiratory system of parturients

Ketamine's ability to maintain Functional Residual Capacity (FRC), minute ventilation, and Tidal Volume (TV) [41] makes it an optimal analgesic/anesthetic agent for parturients because FRC has decreased to 80% of the pre-pregnancy level as the enlarging uterus enters the abdominal cavity. Ketamine is also benifitial to asthmatic parturiets due to its bronchodilatitory property [42]. The laryngeal and pharyngeal reflexes are well maintained during ketamine analgesia/anesthesia provided apnea is avoided.

Although ketamine has a wide therapeutic range, hypersalivation, laryngospasm, and pulmonary aspiration still can't be avoided in ketamine anesthesia [43]. Durieux reported that ketamine inhibited muscarinic receptors in Xenopus oocytes, which might explain some of the anticholinergic effects of ketamine, such as post anesthesia delirum, increased sympathetic tone and bronchodilation [44]. But, inhibition of muscarinic receptors can not explain ketamine induced hypersalivation that is muscarinic stimulatory effect. Therefore, it is unclear that ketamine induces hypersalivation by sympathetic stimulation or by muscarinic receptor activation. Despite the contradictory effect of ketamine on muscarinic receptors, pre-treatment with atropine or glycopyrrolate may decrease ketamine-induced hypersalivation [45,46]. There is no clinical evidence to show decreased salivation will decrease vomiting, laryngospasm and aspiration [46,47]. However, the incidence of laryngospasm with ketamine is much lower than that with other agents. Pooled data have shown that laryngospasm with ketamine requiring intubation occurred in only 0.02% of cases compared with 1.74% of cases performed with anesthetics other than ketamine [48].

Prolonged apnea [49] and arterial hypoxemia [50] have been reported, especially when used with opioids [51]. Respiratory depression of ketamine is related to the infusion dose and rate. When ketamine is i.v. administrated slowly over at least one minue at 1mg/kg to parturients, spontaneous respiration is always preserved [52].

The pharmacodynamic effects of ketamine on Central Nervous System of parturients

Ketamine used to be contraindicated in patients with traumatic brain injury due to its direct cerebral vasodilatory effect, leading to increased Intracranial Pressure (ICP) and reduced intracranial compliance [53,54]. Later, it was found that elevated ICP was a direct result of hypoventilation and hypercarbia [55,56]. Under the condition of controlled ventilation and sedation with thiopental or propofol, ketamine decreased instead of increasing ICP [57,58]. Using target controlled infusion, Bourgoin, et al. showed increase in ketamine concentration from 2.6 ± 2.2 mug/mL to 5.5 ± 3.8 mug/mL did not have a significant change in intracranial pressure, cerebral perfusion pressure, and mean velocity of middle cerebral artery in patient with brain trauma [59]. Ketamine preserved autoregulation and Cerebral Blood Flow (CBF), thus protected the brain near the injured area from ischemia [58]. It has been safely used in brain-injured patients [59]. However, more studies are required before ketamine can be recommended to use routinely in brain injured patients since ketamine may increase the total cerebral blood volume, brain glucose metabolism, and ICP when cerebral compensatory mechanisms have lost [60,61].

Ketamine has been regarded as a proconvulsant since it produces epileptiform patterns on Electroencephalography (EEG), expressed as reduced alpha wave activity, and increased beta, delta and theta wave activities in limbic and thalamic regions [62]. However, early clinical observations that ketamine induced electric seizure activities in epileptic patients [63] and convulsions in healthy patients [64] have never been confirmed [65]. Instead, ketamine successfully treated seizures induced by NMDA [66] or electrical stimulation [67], and stopped refractory status epilepticus [68,69]. Although there are controversial and conflicting data on ketamine induced epileptic activity, it is probably a more anticonvulsant than proconvulsant [70]. After prolonged seizure activities, the synaptic GABAA receptors are rapidly internalized within neurons, resulting in loss of the GABA-mediated synaptic inhibition [71]. Meanwhile, concomitant excitatory glutamate receptors are mobilized to the cell surface, creating a self-sustaining epilepticus cycle [72]. Therefore, GABAergic agents, such as benzodiazepines, barbiturates, or propofol become less effective and larger dosages are required in the lat-

er stage of refractory status epilepticus, which in turn attributes to a high incidence of complications, including hypotension and endotracheal intubation. Series of clinical case reports have demonstrated that ketamine not only controlled seizures rapidly [68,73-76], but also provided stable hemodynamics and minimized respiratory depression [68,76]. Recently, ketamine has been recommended for prevention and treatment of perioperative drug-induced seizures in epileptic patients [70].

Pharmacokinetics of Ketamine in Parturients

Current commercially available ketamine (Ketalar® used in the United States and China) is comprised of equal concentration of R (-) ketamine and its enantiomer S (+) ketamine. Although S (+) ketamine has four times higher affinity for NMDA receptor than R (-) ketamine [77], most of the published pharmacological studies of ketamine have been conducted with racemic mixture of ketamine [20]. This review does not specifically differenciate S (+) -enantiomer from R (-)-enantiomer.

Ketamine can be administered by multiple routes: i.v, i.m., oral, sublingual, intranasal, intrarectal and neuraxial. Recently, peripheral local injection of ketamine or topical application in the forms of gel or cream obtained favorable outcomes as well [78]. The induction doses of ketamine for GA are 10 mg/kg, 6-10 mg/kg, 2-4 mg/kg and 0.5-2 mg/kg for rectal, oral, i.m. and i.v. administration, with onset time of 7-15 mins, 15-20 mins, 3-4 mins, and 15-30 seconds, respectively [79]. Ketamine is rapidly absorbed after i.m. injection with about 93% of bioavailability. The bioavailability of ketamine administered via other routes is generally below 50% [20]. Compared with i.v.or i.m. injection, higher dose of ketamine is required via oral or rectal administration because of the first-pass metabolism and lower absorption. In OB anesthesia, i.v. ketamine is mostly used.

Ketamine is lipophilic and rapidly distributed into the brain and other well-perfused tissues. Ketamine is mostly metabolized by liver P450 microsomal enzyme system to norketamine (80%) and further metabolized to 6-hydroxy-norketamine (15%) then excreted through urine [80]. Another 5% of metabolites, hydroxy-ketamine is a directly transformed product from ketamine, which does not involve the liver metabolism [80,81]. Clearance of ketamine is 20% higher in women than in men [82].

Ketamine was widely used in OB anesthesia for many years after its invention, but there has been little pharmacokinetic data about ketamine in parturient and fetus. An early animal study demonstrated that ketamine crossed the placenta so rapidly that it reached peak plasma concentration in fetus about 1 min after i.v. administration, with a rapid decline in 5 mins [83]. This can be explained by high liposolubility [80] and low plasma pro-

tein binding of ketamine, about 10-30% [84]. Pregnancy may have litter influences on the pharmacokinetics of ketamine, as no differences in the plasma concentration were found between pregnant and non-pregnant ewes or singleton and twin ewes after ketamine i.v. injection [85].

The Pharmacodynamic Effects of Ketamine on Fetus and Developing Brain

Early animal studies have suggested that the fetus can adapt temporarily to decreased Uterine Blood Flow (UBF) by redistributing its cardiac output to the cerebral cortex. While both i.v. and inhalational anesthetics inhibit this compensatory ability [86-88], ketamine has the least suppressive effects on fetus because of its ability to raise maternal BP and UBF [89-91], so that babies delivered shortly after low dose of ketamine might have benefited from an improvement in uterine perfusion. Clinical experiences have demonstrated that ketamine is safe for fetus and neonate in OB anesthesia. Ketamine at < 2 mg/kg i.v. injected in parturient does not depresss the neonates assessed by Apgar scores [92,93]. In a study using ketamine as a sole anesthetic for CD, placental perfusion, as judged by umbilical cord blood-gas status, was well maintained [92]. This makes ketamine an attractive anesthetic in OB anesthesia, even in cases of severe fetal distress [94].

When ketamine is i.v. injected at ≥ 2 mg/kg, fetal depression might occur [95,96]. But this depression was also inversely related to the Induction to Delivery (I-D) interval [95]. I-D interval more than 10 mins and Uterine Incison to Delivery (U-D) interval more than 90 s were associated with fetal hypoxia [93,97,98]. It is generally accepted that i.v. ketamine used at 1-1.5 mg/kg produced normal Apgar scores and unaltered neonatal oxygenation and acid-base balance either in VD or in CD [52,92,93,99,100].

Ketamine is widely used in pediatric anesthesia [101]. Recently, the potential neurotoxicity of ketamine on fetus has raised some concerns [102,103]. The vulnerable window of nervous system development begins at mid-gestation and continues for 2 to 3 years after birth. Ketamine induces apoptosis or programmed cell death in pre- and postnatal neurons in animal studies [16,104]. The possible mechanisms of ketamine neurotoxity are compensatory NMDA receptor upregulation after ketamine exposure, which renders neurons bearing these receptors more susceptible to the excitotoxic effects of endogenous glutamate, and dysregulation of calcium signaling with increased oxidative stress [105,106]. Ketamine also inhibited Neural Stem Progenitor Cells (NSPC) proliferation and enhanced NSPC differentiation [107]. However, we caution that these animal data can not be extrapolated to clinical settings. First, ketamine doses and exposure time used to cause neurodegeneration in most animal studies are seven to ten folds greater than that used in clinical practice. Second, although some animal studies indicated that exposure to ketamine at clinically relevant doses reduced cell proliferation in the offsprings, the current evidences about neurodegeneration produced by ketamine are all collected from intact animals without noxious stimuli. Clinical use of ketamine is usually followed by a surgical or procedural stress, and ketamine may be neurotoxic to the immature CNS in the absence of noxious stimuli but neuroprotective in the same brains in the presence of strong painful stimuli [108]. Studies have demonstrated that under the stress such as pain, hypoxia and ischemia, excessive glutamate was released to produce the necrosis of developing brain, and ketamine mitigated this neurotoxicity by blocking excitatory effect of glutamate [109,110]. Third, ketamine is neuroprotective by inhibiting both nociceptive inflammatory factors [111] and brain derived neurotrophic factors [112]. Anesthetic doses of ketamine prevented the stress-induced impairment of learning and memory in developing rodents [112]. A study on human infants suggested possible neurotoxicic effect on developing brain after repeated ketamine anesthesia [113], but there is no human study about the effect of ketamine on developing fetal brain and neonate cognitive and behavior development, especially long term outcomes, when parturients received ketamine analgesia or anesthesia during pregnancy. More research is required to thoroughly evaluate the effects of ketamine on developing brain.

Clinical use of ketamine in OB patients

Pain management of ketamine

Low-dose ketamine has been used in OB population for pain control during labor, intraoperative rescue analgesia and postoperative pain management.

Intravenous ketamine: Ketamine was used for labor analgesia before epidural technique became popular. It has been reported that 0.25-1 mg/kg of single dose i.v. ketamine used in healthy parturients for VD, with mothers breathing room air, did not have adverse consequences in maternal Arterial Blood Gas (ABG) profiles and neonatal Apgar scores compared with control patients who delivered under spinal anesthesia [52]. Recently, continuous infusion of ketamine with a loading dose of 0.2 mg/kg over 30 mins at the onset of labor pain, followed by an infusion of 0.2 mg/kg/h until delivery of the baby provided significant pain relief without jeoperdizing neonates [114]. A 0.3 mg/lb (0.66 mg/kg) of ketamine i.v. injected just before episiotomy also provided satisfactory surgical anesthesia without adverse outcomes [115]. While labor epidural analgesia is considered a standard of care in developed countries, these protocols may be more practical in developing countries where labor epidural analgesia is not readily

available or when epidural analgesia is contraindicated. Remifentanil has been used for labor analgesia [116] in cases that epidural analgesia is contraindicated, but respiratory depression [117] and cardiac arrest [118] have been reported with its use. Ketamine provides analgesia with the advantage of not depressing respiration. More research is required to compare the safety and efficiency of i.v. ketamine and remifentanil for labor analgesia.

Ketamine is also used as a rescue analgesic during neuroaxial anesthesia for CD. Although spinal anesthesia is excellent for lower abdominal surgery, the failure rate of spinal anesthesia is about 3.2% [119]. In order to avoid GA, some anesthesia providers inject i.v. ketamine at 5-10 mg or 0.2 to 0.4 mg/kg increments to supplement incomplete spinal or epidural block during CD [120]. However, we did not discover studies on dose finding, analgesic effect and side effects of this practice.

Another advantage of i.v. low-dose ketamine is to provide preemptive analgesia. It was reported that small dose of i.v. ketamine, generally 10 mg or 0.15mg/kg, improved postoperative pain control and decreased morphine consumption in 24h-1w after surgery for parturients undergoing either spinal anesthesia [12] or GA [13]. It is noted that ketamine should be given before skin incision as the preemptive analgesia of ketamine takes effect only before NMDA receptors have been sensitized by noxious stimulation [13].

Neuraxial ketamine

Subarachnoid administration of ketamine: Ketamine possesses local anesthetic property [1]. The first intrathecal ketamine as a sole anesthetic agent was studied by Bion in trauma patients for lower extremity surgery [121]. After intrathecal injection 50 mg of ketamine, the mean onset time was 1.7 mins (range 1-4 mins) with peak anesthesia effect achieved at 5-7 mins. Although the duration of adequate surgical anesthesia last for a mean 58 mins (range 45-90 mins), postoperative analgesia went beyond anesthesia for 1 to 3 hrs after sensory recovery [121]. Compared with 25 µg of fentanyl, addition of 0.05 mg/kg of ketamine to 10 mg of 0.5% plain bupivacaine in spinal anesthesia for CD did not seem to have much benefit except for a faster onset of blockade, but at the price of shorter duration [122]. Based on literature review, we do not think subarachnoid ketamine has any advantage over currently used local anesthetics in modern obstretric anesthesia.

Epidural administration of ketamine: The postoperative pain relief achieved with epidural administration of ketamine was first evaluated by Islas [123]. This was demonstrated by another study that preoperative epidural injection of 0.5 mg/kg ketamine produced more effective postoperative analgesia than i.v. injection of the same amount of ketamine [124]. After single i.v. or epidural injection of 0.5 mg/kg ketamine, peak plasma concentration of both routes reached at 20 mins after administration with 0.588 ± 0.208 µg/ml in epidural group and 1.925 ± 0.149 µg/ml in i.v. group. Although ketamine plasma concentrations were lower at 1 and 5 mins after epidural administration than after i.v. injection, concentrations after epidural ketamine were thereafter significantly higher from 90-240 mins after administration, and elimination half life of epidural ketamine (102.95 ± 20.10 mins) was longer compared with i.v. injection (62.54 ± 14.93 mins) [124]. Ketamine is a very lipid soluble drug which is transferred rapidly into the CSF, spinal cord and nerve root vasculature. Slower release from the lipid components of the spinal cord explains its longer elimination half-life and prolonged analgesic effects after epidural administration [124].

The study results of analgesic benefit of epidural ketamine are conflicting. Other researchers found no analgesic effect of epidural ketamine alone [125,126]. Later studies used ketamine as an adjunct to epidural opioids and/or local anesthetics [126-129]. Wong [126] studied patients undergoing major joint replacement and found that epidural ketamine (10 mg or 30 mg) itself did not have analgesic effect compared with 2 mg of epidural morphine, but co-administration of low dose ketamine (10 mg) with low dose morphine (0.5 mg) produced stronger analgesia than 2 mg of epidural morphine alone. Similar result was obtained in patient undergoing lower abdominal surgery. Compared with Patient Controlled Epidural Analgesia (PCEA) with morphine alone, addition of low dose ketamine (5 mg bolus followed by 0.5 mg/h infusion and 0.5 mg per bolus) provided better postoperative pain relief with a lesser amount of morphine and fewer side effects [127]. Therefore, low dose ketamine potentiated analgesic effect of morphine, and reduced its requirement and side effects. When added to local anesthetics, ketamine demonstrated a similar potentiated analgesic effect. In patients who underwent unilateral knee arthroplasty, epidural administration of 0.25 mg/kg of ketamine 10 mins before incision reduced postoperative ropivacaine consumption in epidural analgesia for 48 hrs [128]. Moreover, addition of 25 mg of ketamine to bupivacaine shortened onset time of epidural anesthesia [129].

Studies on epidural ketamine in OB anesthesia/analgesia do not exist. Considering the safety profile of ketamine in OB anesthesia and practice of extra-low concentration of local anesthetics for labor analgesia [130], "extra-low" concentrations of both ketamine (such as 5-10 µg/kg/min epidural infusion) and loca anesthetic may provide good labor analgesia and reduce side effects of both drugs. Future studies are needed to test this hypothesis.

Toxicity of neuraxial ketamine: The potential neurotoxicity has been a concern when neuraxial ketamine is used clinically. Animal studies of spinal cord damage by intrathecally administered ketamine reported

conflicting results [131,132]. Moreover, it has been demonstrated that the preservatives, not ketamine, was the culprit to cause spinal cord injury [133]. So, it is recommended that intrathecal ketamine must be administered in preservative free solution to avoid neurotoxic effects [134]. Epidural ketamine seemed to be safer than intrathecal ketamine. Animal study [135] and numerous clinical studies [136] have not shown spinal damage or clinical evidence of neurological toxicities with epidural ketamine.

Ketamine use in general anesthesia: Early experience with the standard i.v. induction dose of ketamine (2.0 mg/kg) for CD [95] and VD [5] was associated with a high incidence of maternal complications and neonatal depression. Downing JW, et al. [95] reported an incidence of 20% of nausea and vointing, and 10% of hallucination. Sixteen percent (8/50) of neonatal depression occurred with Apgar minus color (A-C) scores less than 5-6/8 two minutes after birth. However, all neonates were in good condition 24 hrs after delivery. These adverse effects could be attenuated by using low dose of ketamine (1.5 mg/kg) as long as the I-D time < 10 mins and U-D time < 90 s [93].

Although propfol is currently most used for induction of GA for CD, the hemodynamic advantage makes ketamine a preferred induction agent of GA for hypovolemic and hypotensive parturients like placenta abruption or uterine rupture. Ketamine 1.5 mg/kg can be given to prevent maternal awareness [93] and not to increase uterine tone [137]. Respiratory depression of newborn has not been reported with this induction dose [93]. The documented psychomimetic or dysphoric reactions, even in low dose of ketamine [138] can be prevented or treated with benzodiazepines and more effectively with dexmeditomidine [139]. However, with significant increased blood volume and cardiac workload during pregnancy, any further minor increase of catecholamines could aggrevate cardiac burden, and lead to heart failure and some other deterious consequences in pregnant women who have cardiac disease. Studies on safety of induction regimens containing ketamine are required in parturient with cardiac disease.

Ketamine and breastfeeding

Although no human study concerning about the transfer of ketamine to breast milk [140], there is a suggestion to avoid ketamine during pregnancy and breastfeeding due to lack of safety data [28]. However, women who underwent elective CD under spinal anesthesia and received i.m. ketamine 0.5 mg/kg bolus 10 mins after birth followed by 2 μg/kg/min. i.v. continuous infusion for 12 hrs did not have negative impact on women's ability to breastfeed or breastfeeding duration [141].

Antiemetic effect

Early animal study demonstrated that nausea and vomitimg could be induced by injection of catecholamines into lateral ventricle in the brain [142]. Ketamine may induce nausea and vomitimg due to increased release of endogenous catecholamines [8]. However, recent study has shown that ketamine decreased Intraoperative Nausea and Vomiting (IONV) during CD under spinal anesthesia by counteracting hypotension, visceral pain and vagal stimulation. Shabana, et al. reported that preoperative i.v. ketamine 0.5 mg/Kg reduced the incidence of IONV from 40.9% to 20.9% [143]. Two recent comprehensive meta analyses showed that the addition of ketamine to opioids based patient-controlled analgesia significantly attenuated Postoperative Nausea and Vomiting (PONV) by decreasing opioid consumption [9,10]. More research are required to compare the antiemtic efficacy of ketamine with current vasopressors, such as ephedrine.

Shivering prevention

Ketamine has sympathetic stimulation and vasoconstrictive effects, which not only decrease the incidence of hypotension and use of vasoactive pressors, but also reduce the shivering during spinal anesthesia. An i.v. dose of 0.25 mg/kg was as effective as 0.5 mg/kg of ketamine in preventing shivering of parturients under spinal anesthesia with less side effects [144].

Ketamine in preeclampsia and eclampsia

Dysfunction of maternal immune system leads to increased pro-inflammatory immune cells and cytokines, such as TNF-α, IL-6 and IL-17 and decreased regulatory immune cells and cytokines IL-10 and IL-4, which creates a chronic and uncontrolled state of inflammation. This immune imbalance is believed to be part of the pathophysiology associated with preeclampsia [145]. MRI study indicated that relative cerebral ischemia existed in preeclamptic patients [146]. Ketamine has anti-inflammatory effects and decreases the levels of TNF-α, IL 6 and 8 [32-35]. It also preserved autoregulation and CBF, thus protected the brain near the injured area from ischemia [58]. It remains unknown whether ketamine relieves or aggravates the cerebral ischemia in preeclamptic patient. Although 2 mg/kg of ketamine has been used for hypertensive patient with systolic and diastolic pressures as high as 218 mmHg and 109 mmHg without adverse consequences [147] and low dose ketamine (50 mg) stopped eclamptic convulsions that were refractory to conventional therapy only minimally affected patient BP [148], until more research has demonstrated that the anti-inflammatory and cerebral protective effect of ketamine have benefits in preeclamptic patient, it is prudent not to use ketamine in patient with preeclampsia because of sympathetic stimulation and possible worsening of hypertension.

Rucci and Caroli reported that ketamine successfully aborted seizures without adverse effects in two eclamptic patients using a single i.v. dose of 25 mg, and then maintained on a daily dose of 50- 250 mg [148]. However, currently there are not enough evidence to support routine use ketamine to stop epileptic attacks in eclamptic patient. The decision to use ketamine in those parturients should be on case by case basis and more studies are needed.

Antidepressant effect

The antidepressant effect of ketamine has been well known since the early time of clinical use [42]. Subanesthetic dose of ketamine (0.5-1 mg/kg) produced a "high" feeling in volunteers and seemed to be anxiolytic at smaller dosages [149]. A 0.5 mg/kg ketamine infusion over 40 mins significantly improved the symptoms of depressed patients within 72 hrs [150].

Postpartum Depression (PPD) is the most common mood disorder of new mothers, which has negative impact on both mother-baby bonding and baby's wellbeing and development. About 25% of women suffer PPD in the first 3 months after delivery [151]. Studies have shown that good labor pain control decreased incidence of PPD in one week [152] and one year [153] after childbirth. Ketamine has both analgesic and antidepressive properties. Parturient might have more benefit from adding ketamine in their labor analgesic regimen. Interestingly, a recent study has found that the ketamine metabolite Hydroxynorketamine (HNK), not ketamine itself, is responsible for the antidepressive effect of ketamine [154]. Decreased the metabolism of ketamine to HNK reduced the effectiveness of ketamine antidepressive effect in mice. Futhermore, treating animals with HNK produced the same rapid and sustained antidepressant-like effects as treatment with ketamine. These researchers also showed that a lower dose of ketamine is needed to reduce depression-like behaviors in females than in males and the levels of HNK were several fold higher in the brains of females than males after the animals were given the same dose of the drug [154]. It is intriguing to see the study of the effect of ketamine on PPD before HNK is on the market as an antidepressant.

Summary

Ketamine, a noncompetitive NMDA receptor antagonist, was widely used in OB anesthesia and labor analgesia before neuraxial analgesia/anesthesia became safe, effective and popular. Researches in the last 2 decades have shown that subanesthetic doses of ketamine possess excellent analgesic effect, which resulted in more and more clinical use and research in non-obstetric patient. However, studies of ketamine in OB population is far behind. One of the reasons for this lack of research in OB patient may be a safety concern, but previous clinical experiences have demonstrated that i.v. ketamine ≤ 1.5 mg/kg and low dose neuraxial ketamine are safe to both mother and baby. Use of ketamine in OB anesthesia has reappeared. More researches are needed to demonstrate ketamine can add more benefit for our OB patients. Based on current literature, we recapitulate:

1. Induction of GA with 1-1.5 mg/kg i.v. ketamine in asthmatic or hypotensive pregnant women is a reasonable choice and safe.

2. A few studies showed promising result of i.v. ketamine for labor analgesia. More studies are required to evaluate the safety and efficacy of i.v. ketamine against currently used i.v. pain medications, such as remifentanil, in parturients since it is a feasible pain management modality in places where epidural analgesia is unavailable and when neuraxial analgesia is contraindicated.

3. No evidence supports that ketamine has any advantage over currently used local anethetics in spinal anesthesia.

4. Epidural ketamine has synergistic analgesic effect with epidural opioids and local anesthetics in non-obstetric patients. Data on epidural ketamine in labor analgesia and post operative pain control in OB patient are lacking. Future study on "extra-low" concentation of epidural ketamine in OB patient with same definition and standardized protocol may provide new labor analgesic method.

5. Application of ketamine in patients with unsatisfied neuraxial anesthesia during CD, preeclampsia/eclampsia, and in other clinical settings, such as effect on breastfeeding, prevention of IONV/PONV, shivering and PPD is also worth further investigation.

6. The Study results of ketamine neurotoxic/neuroprotective effect on developing brain are conflicting and evolving.

Corresponding Author: *Peishan Zhao, Department of Anesthesiology, Tufts Medical Center, Tufts University School of Medicine, 800 Washington Street, #298 Boston, MA 02111, USA, Fax: 617-636-8384, Tel: 617-636-6044, E-mail: pzhao@tuftsmedicalcenter.org*

References

1. Sinner B, Graf BM: Ketamine. Handbook of experimental pharmacology 2008(182):313-333.

2. Domino EF, Chodoff P, Corssen G: Pharmacologic Effects of Ci-581, a New Dissociative Anesthetic, in Man. Clinical pharmacology and therapeutics 1965, 6:279-291.

3. Chodoff P, Stella JG: Use of CI-581 a phencyclidine derivative for obstetric anesthesia. Anesthesia and analgesia 1966, 45(5):527-530.

4. Liu F, Paule MG, Ali S, Wang C: Ketamine-induced neurotoxicity and changes in gene expression in the developing rat brain. Current neuropharmacology 2011, 9(1):256-261.

5. Corssen G: Ketamine in obstetric anesthesia. Clinical obstetrics and gynecology 1974, 17(2):249-258.

6. White PF, Way WL, Trevor AJ: Ketamine--its pharmacology and therapeutic uses. Anesthesiology 1982, 56(2):119-136.

7. Ghoneim MM, Hinrichs JV, Mewaldt SP, Petersen RC: Ketamine: behavioral effects of subanesthetic doses. Journal of clinical psychopharmacology 1985, 5(2):70-77.

8. Watcha MF, White PF: Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992, 77(1):162-184.

9. 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(12):2854-2864.

10. 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. Canadian journal of anaesthesia 2016, 63(3):311-325.

11. Heesen M, Bohmer J, Brinck EC, Kontinen VK, Klohr S, Rossaint R, Straube S: Intravenous ketamine during spinal and general anaesthesia for caesarean section: systematic review and meta-analysis. Acta anaesthesiologica Scandinavica 2015, 59(4):414-426.

12. Menkiti ID, Desalu I, Kushimo OT: Low-dose intravenous ketamine improves postoperative analgesia after caesarean delivery with spinal bupivacaine in African parturients. International journal of obstetric anesthesia 2012, 21(3):217-221.

13. Ngan Kee WD, Khaw KS, Ma ML, Mainland PA, Gin T: Postoperative analgesic requirement after cesarean section: a comparison of anesthetic induction with ketamine or thiopental. Anesthesia and analgesia 1997, 85(6):1294-1298.

14. Spandou E, Karkavelas G, Soubasi V, Avgovstides-Savvopoulou P, Loizidis T, Guiba-Tziampiri O: Effect of ketamine on hypoxic-ischemic brain damage in newborn rats. Brain research 1999, 819(1-2):1-7.

15. Bhutta AT: Ketamine: a controversial drug for neonates. Seminars in perinatology 2007, 31(5):303-308.

16. Slikker W, Jr., Zou X, Hotchkiss CE, Divine RL, Sadovova N, Twaddle NC, Doerge DR, Scallet AC, Patterson TA, Hanig JP et al: Ketamine-induced neuronal cell death in the perinatal rhesus monkey. Toxicological sciences : an official journal of the Society of Toxicology 2007, 98(1):145-158.

17. Zou X, Patterson TA, Divine RL, Sadovova N, Zhang X, Hanig JP, Paule MG, Slikker W, Jr., Wang C: Prolonged exposure to ketamine increases neurodegeneration in the developing monkey brain. International journal of developmental neuroscience 2009, 27(7):727-731.

18. Reich DL, Silvay G: Ketamine: an update on the first twenty-five years of clinical experience. Canadian journal of anaesthesia 1989, 36(2):186-197.

19. Kohrs R, Durieux ME: Ketamine: teaching an old drug new tricks. Anesthesia and analgesia 1998, 87(5):1186-1193.

20. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI: Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. Clinical pharmacokinetics 2016, 55(9):1059-1077.

21. Meng L, Li J, Lu Y, Sun D, Tao YX, Liu R, Luo JJ: Ketamine - A Multifaceted Drug. Translational perioperative and pain medicine 2015, 1(2):20-26.

22. Anis NA, Berry SC, Burton NR, Lodge D: The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. British journal of pharmacology 1983, 79(2):565-575.

23. Orser BA, Pennefather PS, MacDonald JF: Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors. Anesthesiology 1997, 86(4):903-917.

24. 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):111-125.

25. Jouguelet-Lacoste J, La Colla L, Schilling D, Chelly JE: The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Pain medicine 2015, 16(2):383-403.

26. Grant IS, Nimmo WS, Clements JA: Pharmacokinetics and analgesic effects of i.m. and oral ketamine. British journal of anaesthesia 1981, 53(8):805-810.

27. Vadivelu N, Schermer E, Kodumudi V, Belani K, Urman RD, Kaye AD: Role of ketamine for analgesia in adults and children. Journal of anaesthesiology, clinical pharmacology 2016, 32(3):298-306.

28. Aroni F, Iacovidou N, Dontas I, Pourzitaki C, Xanthos T: Pharmacological aspects and potential new clinical applications of ketamine: reevaluation of an old drug. Journal of clinical pharmacology 2009, 49(8):957-964.

29. Coates KM, Flood P: Ketamine and its preservative, benzethonium chloride, both inhibit human recombinant alpha7 and alpha4beta2 neuronal nicotinic acetylcholine receptors in Xenopus oocytes. British journal of pharmacology 2001, 134(4):871-879.

30. Pacheco Dda F, Romero TR, Duarte ID: Central antinociception induced by ketamine is mediated by endogenous opioids and mu- and delta-opioid receptors. Brain research 2014, 1562:69-75.

31. Hustveit O, Maurset A, Oye I: Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. Pharmacology & toxicology 1995, 77(6):355-359.

32. Roytblat L, Talmor D, Rachinsky M, Greemberg L, Pekar A, Appelbaum A, Gurman GM, Shapira Y, Duvdenani A: Ketamine attenuates the interleukin-6 response after cardiopulmonary bypass. Anesthesia and analgesia 1998, 87(2):266-271.

33. Weiss M, Birkhahn A, Mettler S, Schneider M, Wernet P: Stereoselective suppression of neutrophil function by ketamine? Immunopharmacology and immunotoxicology 1995, 17(1):91-107.

34. Schmidt H, Ebeling D, Bauer H, Bach A, Bohrer H, Gebhard MM, Martin E: Ketamine attenuates endotoxin-induced leukocyte adherence in rat mesenteric venules. Critical care medicine 1995, 23(12):2008-2014.

35. Sun J, Zhou ZQ, Lv R, Li WY, Xu JG: Ketamine inhibits LPS-induced calcium elevation and NF-kappa B activation in monocytes. Inflammation research 2004, 53(7):304-308.

36. Sprenger T, Valet M, Woltmann R, Zimmer C, Freynhagen R, Kochs EF, Tolle TR, Wagner KJ: Imaging pain modulation by subanesthetic S-(+)-ketamine. Anesthesia and analgesia 2006, 103(3):729-737.

37. Denda S, Shimoji K, Tomita M, Baba H, Yamakura T, Masaki H, Endoh H, Fukuda S: Central nuclei and spinal pathways in feedback inhibitory spinal cord potentials in ketamine-anaesthetized rats. British journal of anaesthesia 1996, 76(2):258-265.

38. Tweed WA, Minuck M, Mymin D: Circulatory responses to ketamine anesthesia. Anesthesiology 1972, 37(6):613-619.

39. Kaye AD, Banister RE, Anwar M, Feng CJ, Kadowitz PJ, Nossaman BD: Pulmonary vasodilation by ketamine is mediated in part by L-type calcium channels. Anesthesia and analgesia 1998, 87(4):956-962.

40. Kaye AD, Banister RE, Fox CJ, Ibrahim IN, Nossaman BD: Analysis of ketamine responses in the pulmonary vascular bed of the cat. Critical care medicine 2000, 28(4):1077-1082.

41. Shulman D, Beardsmore CS, Aronson HB, Godfrey S: The effect of ketamine on the functional residual capacity in young children. Anesthesiology 1985, 62(5):551-556.

42. Domino EF: Taming the ketamine tiger. 1965. Anesthesiology 2010, 113(3):678-684.

43. Penrose BH: Aspiration pneumonitis following ketamine induction for general anesthesia. Anesthesia and analgesia 1972, 51(1):41-43.

44. Durieux ME: Inhibition by ketamine of muscarinic acetylcholine receptor function. Anesthesia and analgesia 1995, 81(1):57-62.

45. Toft P, Romer UD: Glycopyrrolate compared with atropine in association with ketamine anaesthesia. Acta anaesthesiologica Scandinavica 1987, 31(5):438-440.

46. Heinz P, Geelhoed GC, Wee C, Pascoe EM: Is atropine needed with ketamine sedation? A prospective, randomised, double blind study. EMJ 2006, 23(3):206-209.

47. Green SM, Roback MG, Krauss B, Emergency Department Ketamine Meta-Analysis Study G: Laryngospasm during emergency department ketamine sedation: a case-control study. Pediatric emergency care 2010, 26(11):798-802.

48. Green SM, Johnson NE: Ketamine sedation for pediatric procedures: Part 2, Review and implications. Annals of emergency medicine 1990, 19(9):1033-1046.

49. van Wijhe M, Stricker BH, Rejger VS: Prolonged apnoea with ketamine. British journal of anaesthesia 1986, 58(5):573-574.

50. Zsigmond EK, Matsuki A, Kothary SP, Jallad M: Arterial hypoxemia caused by intravenous ketamine. Anesthesia and analgesia 1976, 55(3):311-314.

51. Bourke DL, Malit LA, Smith TC: Respiratory interactions of ketamine and morphine. Anesthesiology 1987, 66(2):153-156.

52. Maduska AL, Hajghassemali M: Arterial blood gases in mothers and infants during ketamine anesthesia for vaginal delivery. Anesthesia and analgesia 1978, 57(1):121-123.

53. Evans J, Rosen M, Weeks RD, Wise C: Ketamine in neurosurgical procedures. Lancet 1971, 1(7688):40-41.

54. Gibbs JM: The effect of intravenous ketamine on cerebrospinal fluid pressure. British journal of anaesthesia 1972, 44(12):1298-1302.

55. Pfenninger E, Dick W, Ahnefeld FW: The influence of ketamine on both normal and raised intracranial pressure of artificially ventilated animals. European journal of anaesthesiology 1985, 2(3):297-307.

56. Schwedler M, Miletich DJ, Albrecht RF: Cerebral blood flow and metabolism following ketamine administration. Canadian Anaesthetists' Society journal 1982, 29(3):222-226.

57. Albanese J, Arnaud S, Rey M, Thomachot L, Alliez B, Martin C: Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. Anesthesiology 1997, 87(6):1328-1334.

58. Himmelseher S, Durieux ME: Revising a dogma: ketamine for patients with neurological injury? Anesthesia and analgesia 2005, 101(2):524-534, table of contents.

59. Bourgoin A, Albanese J, Leone M, Sampol-Manos E, Viviand X, Martin C: Effects of sufentanil or ketamine administered in target-controlled infusion on the cerebral hemodynamics of severely brain-injured patients. Critical care medicine 2005, 33(5):1109-1113.

60. Langsjo JW, Kaisti KK, Aalto S, Hinkka S, Aantaa R, Oikonen V, Sipila H, Kurki T, Silvanto M, Scheinin H: Effects of subanesthetic doses of ketamine on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiology 2003, 99(3):614-623.

61. Langsjo JW, Salmi E, Kaisti KK, Aalto S, Hinkka S, Aantaa R, Oikonen V, Viljanen T, Kurki T, Silvanto M et al: Effects of subanesthetic ketamine on regional cerebral glucose metabolism in humans. Anesthesiology 2004, 100(5):1065-1071.

62. Corssen G, Little SC, Tavakoli M: Ketamine and epilepsy. Anesthesia and analgesia 1974, 53(2):319-335.

63. Ferrer-Allado T, Brechner VL, Dymond A, Cozen H, Crandall P: Ketamine-induced electroconvulsive phenomena in the human limbic and thalamic regions. Anesthesiology 1973, 38(4):333-344.

64. Thompson GE: Ketamine-induced convulsions. Anesthesiology 1972, 37(6):662-663.

65. Celesia GG, Chen RC, Bamforth BJ: Effects of ketamine in epilepsy. Neurology 1975, 25(2):169-172.

66. Bennett DA, Bernard PS, Amrick CL: A comparison of PCP-like compounds for NMDA antagonism in two in vivo models. Life sciences 1988, 42(4):447-454.

67. Borris DJ, Bertram EH, Kapur J: Ketamine controls prolonged status epilepticus. Epilepsy research 2000, 42(2-3):117-122.

68. Synowiec AS, Singh DS, Yenugadhati V, Valeriano JP, Schramke CJ, Kelly KM: Ketamine use in the treatment of refractory status epilepticus. Epilepsy research 2013, 105(1-2):183-188.

69. Fang Y, Wang X: Ketamine for the treatment of refractory status epilepticus. Seizure 2015, 30:14-20.

70. Voss LJ, Sleigh JW, Barnard JP, Kirsch HE: The howling cortex: seizures and general anesthetic drugs. Anesthesia and analgesia 2008, 107(5):1689-1703.

71. Goodkin HP, Yeh JL, Kapur J: Status epilepticus increases the intracellular accumulation of GABAA receptors. The Journal of neuroscience 2005, 25(23):5511-5520.

72. Abend NS, Dlugos DJ: Treatment of refractory status epilepticus: literature review and a proposed protocol. Pediatric neurology 2008, 38(6):377-390.

73. Pruss H, Holtkamp M: Ketamine successfully terminates malignant status epilepticus. Epilepsy research 2008, 82(2-3):219-222.

74. Hsieh CY, Sung PS, Tsai JJ, Huang CW: Terminating prolonged refractory status epilepticus using ketamine. Clinical neuropharmacology 2010, 33(3):165-167.

75. Yeh PS, Shen HN, Chen TY: Oral ketamine controlled refractory nonconvulsive status epilepticus in an elderly patient. Seizure 2011, 20(9):723-726.

76. Kofke WA, Bloom MJ, Van Cott A, Brenner RP: Electrographic tachyphylaxis to etomidate and ketamine used for refractory status epilepticus controlled with isoflurane. Journal of neurosurgical anesthesiology 1997, 9(3):269-272.

77. Oye I, Paulsen O, Maurset A: Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. The Journal of pharmacology and experimental therapeutics 1992, 260(3):1209-1213.

78. Sawynok J: Topical and peripheral ketamine as an analgesic. Anesthesia and analgesia 2014, 119(1):170-178.

79. Jolly T, McLean HS: Use of ketamine during procedural sedation: indications, controversies, and side effects. Journal of infusion nursing 2012, 35(6):377-382.

80. Mion G, Villevieille T: Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS neuroscience & therapeutics 2013, 19(6):370-380.

81. Noppers I, Olofsen E, Niesters M, Aarts L, Mooren R, Dahan A, Kharasch E, Sarton E: Effect of rifampicin on S-ketamine and S-norketamine plasma concentrations in healthy volunteers after intravenous S-ketamine administration. Anesthesiology 2011, 114(6):1435-1445.

82. Sigtermans M, Dahan A, Mooren R, Bauer M, Kest B, Sarton E, Olofsen E: S(+)-ketamine effect on experimental pain and cardiac output: a population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. Anesthesiology 2009, 111(4):892-903.

83. Craft JB, Jr., Coaldrake LA, Yonekura ML, Dao SD, Co EG, Roizen MF, Mazel P, Gilman R, Shokes L, Trevor AJ: Ketamine, catecholamines, and uterine tone in pregnant ewes. American journal of obstetrics and gynecology 1983, 146(4):429-434.

84. Dayton PG, Stiller RL, Cook DR, Perel JM: The binding of ketamine to plasma proteins: emphasis on human plasma. European journal of clinical pharmacology 1983, 24(6):825-831.

85. Musk GC, Netto JD, Maker GL, Trengove RD: Transplacental transfer of medetomidine and ketamine in pregnant ewes. Laboratory animals 2012, 46(1):46-50.

86. Palahniuk RJ, Doig GA, Johnson GN, Pash MP: Maternal halothane anesthesis reduces cerebral blood flow in the acidotic sheep fetus. Anesthesia and analgesia 1980, 59(1):35-39.

87. Pickering BG, Palahniuk RJ, Cote J, Wade JG, Pash MG: Cerebral vascular responses to ketamine and thiopentone during foetal acidosis. Canadian Anaesthetists' Society journal 1982, 29(5):463-467.

88. Irestedt L, Lagercrantz H, Hjemdahl P, Hagnevik K, Belfrage P: Fetal and maternal plasma catecholamine levels at elective cesarean section under general or epidural anesthesia versus vaginal delivery. American journal of obstetrics and gynecology 1982, 142(8):1004-1010.

89. Dich-Nielsen J, Holasek J: Ketamine as induction agent for caesarean section. Acta anaesthesiologica Scandinavica 1982, 26(2):139-142.

90. Schultetus RR, Paulus DA, Spohr GL: Haemodynamic effects of ketamine and thiopentone during anaesthetic induction for caesarean section. Canadian Anaesthetists' Society journal 1985, 32(6):592-596.

91. Levinson G, Shnider SM, Gildea JE, DeLorimier AA: Maternal and foetal cardiovascular and acid-base changes during ketamine anaesthesia in pregnant ewes. British journal of anaesthesia 1973, 45(11):1111-1115.

92. Meer FM, Downing JW, Coleman AJ: An intravenous method of anaesthesia for Caesarean section. II. Ketamine. British journal of anaesthesia 1973, 45(2):191-196.

93. Baraka A, Louis F, Dalleh R: Maternal awareness and neonatal outcome after ketamine induction of anaesthesia for Caesarean section. Canadian journal of anaesthesia 1990, 37(6):641-644.

94. Swartz J, Cumming M, Biehl D: The effect of ketamine anaesthesia on the acidotic fetal lamb. Canadian journal of anaesthesia 1987, 34(3 (Pt 1)):233-237.

95. Downing JW, Mahomedy MC, Jeal DE, Allen PJ: Anaesthesia for Caesarean section with ketamine. Anaesthesia 1976, 31(7):883-892.

96. Galbert MW, Gardner AE: Ketamine for obstetrical anesthesia. Anesthesia and analgesia 1973, 52(6):926-930.

97. Little B, Chang T, Chucot L, Dill WA, Enrile LL, Glazko AJ, Jassani M, Kretchmer H, Sweet AY: Study of ketamine as an obstetric anesthetic agent. American journal of obstetrics and gynecology 1972, 113(2):247-260.

98. Baraka A, Louis F, Noueihid R, Diab M, Dabbous A, Sibai A: Awareness following different techniques of general an-

aesthesia for caesarean section. British journal of anaesthesia 1989, 62(6):645-648.

99. Nayar R, Sahajanand H: Does anesthetic induction for Cesarean section with a combination of ketamine and thiopentone confer any benefits over thiopentone or ketamine alone? A prospective randomized study. Minerva anestesiologica 2009, 75(4):185-190.

100. Traub E, Knoche E, Dick W, Volschow E: [Apgar status, blood gases and acid base balance of neonates after caesarean sections, using either thiopentone or ketamine for induction of anaesthesia (author's transl)]. Der Anaesthesist 1977, 26(4):176-183.

101. Schnabel A, Poepping DM, Kranke P, Zahn PK, Pogatzki-Zahn EM: Efficacy and adverse effects of ketamine as an additive for paediatric caudal anaesthesia: a quantitative systematic review of randomized controlled trials. British journal of anaesthesia 2011, 107(4):601-611.

102. Zhao T, Li Y, Wei W, Savage S, Zhou L, Ma D: Ketamine administered to pregnant rats in the second trimester causes long-lasting behavioral disorders in offspring. Neurobiology of disease 2014, 68:145-155.

103. Dong C, Rovnaghi CR, Anand KJ: Ketamine exposure during embryogenesis inhibits cellular proliferation in rat fetal cortical neurogenic regions. Acta anaesthesiologica Scandinavica 2016, 60(5):579-587.

104. Jin J, Gong K, Zou X, Wang R, Lin Q, Chen J: The blockade of NMDA receptor ion channels by ketamine is enhanced in developing rat cortical neurons. Neuroscience letters 2013, 539:11-15.

105. Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vockler J, Dikranian K, Tenkova TI, Stefovska V, Turski L, Olney JW: Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science 1999, 283(5398):70-74.

106. Wang C, Sadovova N, Hotchkiss C, Fu X, Scallet AC, Patterson TA, Hanig J, Paule MG, Slikker W, Jr.: Blockade of N-methyl-D-aspartate receptors by ketamine produces loss of postnatal day 3 monkey frontal cortical neurons in culture. Toxicological sciences 2006, 91(1):192-201.

107. Dong C, Rovnaghi CR, Anand KJ: Ketamine alters the neurogenesis of rat cortical neural stem progenitor cells. Critical care medicine 2012, 40(8):2407-2416.

108. Liu JR, Liu Q, Li J, Baek C, Han XH, Athiraman U, Soriano SG: Noxious stimulation attenuates ketamine-induced neuroapoptosis in the developing rat brain. Anesthesiology 2012, 117(1):64-71.

109. Church J, Zeman S, Lodge D: The neuroprotective action of ketamine and MK-801 after transient cerebral ischemia in rats. Anesthesiology 1988, 69(5):702-709.

110. Anand KJ, Garg S, Rovnaghi CR, Narsinghani U, Bhutta AT, Hall RW: Ketamine reduces the cell death following inflammatory pain in newborn rat brain. Pediatric research 2007, 62(3):283-290.

111. Wang CQ, Ye Y, Chen F, Han WC, Sun JM, Lu X, Guo R, Cao K, Zheng MJ, Liao LC: Posttraumatic administration of a sub-anesthetic dose of ketamine exerts neuroprotection via attenuating inflammation and autophagy. Neuroscience 2016, 343:30-38.

112. Peng S, Zhang Y, Wang H, Ren B, Zhang J: Anesthetic ketamine counteracts repetitive mechanical stress-induced learning and memory impairment in developing mice. Molecular biology reports 2011, 38(7):4347-4351.

113. Yan J, Li YR, Zhang Y, Lu Y, Jiang H: Repeated exposure to anesthetic ketamine can negatively impact neurodevelopment in infants: a prospective preliminary clinical study. Journal of child neurology 2014, 29(10):1333-1338.

114. Joel S, Joselyn A, Cherian VT, Nandhakumar A, Raju N, Kaliaperumal I: Low-dose ketamine infusion for labor analgesia: A double-blind, randomized, placebo controlled clinical trial. Saudi journal of anaesthesia 2014, 8(1):6-10.

115. Janeczko GF, el-Etr AA, Younes S: Low-dose ketamine anesthesia for obstetrical delivery. Anesthesia and analgesia 1974, 53(6):828-831.

116. Evron S, Glezerman M, Sadan O, Boaz M, Ezri T: Remifentanil: a novel systemic analgesic for labor pain. Anesthesia and analgesia 2005, 100(1):233-238.

117. Muchatuta NA, Kinsella SM: Remifentanil for labour analgesia: time to draw breath? Anaesthesia 2013, 68(3):231-235.

118. Marr R, Hyams J, Bythell V: Cardiac arrest in an obstetric patient using remifentanil patient-controlled analgesia. Anaesthesia 2013, 68(3):283-287.

119. Visser WA: Spinal anesthesia failure after local anesthetic injection into cerebrospinal fluid. Regional anesthesia and pain medicine 2011, 36(6):631.

120. Chestnut DH: Obstetric Anesthesia; 2014. 5th edition, Chapters 22, P26

121. Bion JF: Intrathecal ketamine for war surgery. A preliminary study under field conditions. Anaesthesia 1984, 39(10):1023-1028.

122. Unlugenc H, Ozalevli M, Gunes Y, Olguner S, Evruke C, Ozcengiz D, Akman H: A double-blind comparison of intrathecal S(+) ketamine and fentanyl combined with bupivacaine 0.5% for Caesarean delivery. European journal of anaesthesiology 2006, 23(12):1018-1024.

123. Islas JA, Astorga J, Laredo M: Epidural ketamine for control of postoperative pain. Anesthesia and analgesia 1985, 64(12):1161-1162.

124. Xie H, Wang X, Liu G, Wang G: Analgesic effects and pharmacokinetics of a low dose of ketamine preoperatively administered epidurally or intravenously. The Clinical journal of pain 2003, 19(5):317-322.

125. Ravat F, Dorne R, Baechle JP, Beaulaton A, Lenoir B, Leroy P, Palmier B: Epidural ketamine or morphine for postoperative analgesia. Anesthesiology 1987, 66(6):819-822.

126. Wong CS, Liaw WJ, Tung CS, Su YF, Ho ST: Ketamine potentiates analgesic effect of morphine in postoperative epidural pain control. Regional anesthesia 1996, 21(6):534-541.

127. Tan PH, Kuo MC, Kao PF, Chia YY, Liu K: Patient-controlled epidural analgesia with morphine or morphine plus ketamine for post-operative pain relief. European journal of anaesthesiology 1999, 16(12):820-825.

128. Himmelseher S, Ziegler-Pithamitsis D, Argiriadou H, Martin J, Jelen-Esselborn S, Kochs E: Small-dose S(+)-ketamine reduces postoperative pain when applied with ropivacaine in epidural anesthesia for total knee arthroplasty. Anesthesia and analgesia 2001, 92(5):1290-1295.

129. Yanli Y, Eren A: The effect of extradural ketamine on onset time and sensory block in extradural anaesthesia with bupivacaine. Anaesthesia 1996, 51(1):84-86.

130. Stoddart AP, Nicholson KE, Popham PA: Low dose bupivacaine/fentanyl epidural infusions in labour and mode of delivery. Anaesthesia 1994, 49(12):1087-1090.

131. Borgbjerg FM, Svensson BA, Frigast C, Gordh T, Jr.: Histopathology after repeated intrathecal injections of preservative-free ketamine in the rabbit: a light and electron microscopic examination. Anesthesia and analgesia 1994, 79(1):105-111.

132. Vranken JH, Troost D, de Haan P, Pennings FA, van der Vegt MH, Dijkgraaf MG, Hollmann MW: Severe toxic damage to the rabbit spinal cord after intrathecal administration of preservative-free S(+)-ketamine. Anesthesiology 2006, 105(4):813-818.

133. Malinovsky JM, Lepage JY, Cozian A, Mussini JM, Pinaudt M, Souron R: Is ketamine or its preservative responsible for neurotoxicity in the rabbit? Anesthesiology 1993, 78(1):109-115.

134. Hodgson PS, Neal JM, Pollock JE, Liu SS: The neurotoxicity of drugs given intrathecally (spinal). Anesthesia and analgesia 1999, 88(4):797-809.

135. Acosta A, Gomar C, Bombi JA, Graca DL, Garrido M, Krauspenhar C: Ultrastructure of canine meninges after repeated epidural injection of S(+)-ketamine. Regional anesthesia and pain medicine 2006, 31(5):438-444.

136. Subramaniam K, Subramaniam B, Steinbrook RA: Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesthesia and analgesia 2004, 99(2):482-495, table of contents.

137. Oats JN, Vasey DP, Waldron BA: Effects of ketamine on the pregnant uterus. British journal of anaesthesia 1979, 51(12):1163-1166.

138. Ahern TL, Herring AA, Anderson ES, Madia VA, Fahimi J, Frazee BW: The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. The American journal of emergency medicine 2015, 33(2):197-201.

139. Levanen J, Makela ML, Scheinin H: Dexmedetomidine premedication attenuates ketamine-induced cardiostimulatory effects and postanesthetic delirium. Anesthesiology 1995, 82(5):1117-1125.

140. Cobb B, Liu R, Valentine E, Onuoha O: Breastfeeding after Anesthesia: A Review for Anesthesia Providers Regarding the Transfer of Medications into Breast Milk. Translational perioperative and pain medicine 2015, 1(2):1-7.

141. Suppa E, Valente A, Catarci S, Zanfini BA, Draisci G: A study of low-dose S-ketamine infusion as "preventive" pain treatment for cesarean section with spinal anesthesia: benefits and side effects. Minerva anestesiologica 2012, 78(7):774-781.

142. Jenkins LC, Lahay D: Central mechanisms of vomiting related to catecholamine response: anaesthetic implication. Canadian Anaesthetists' Society journal 1971, 18(4):434-441.

143. A.M. Shabana ESN, H.E. Moawad: Effect of examine on intraoperative nausea and vomiting during elective caesarean section under spinal anaesthesia: A placebo-controlled prospective randomized double blinded study. Egyptian Journal of Anaesthesia 2012, 28(2):169–174.

144. Kose EA, Honca M, Dal D, Akinci SB, Aypar U: Prophylactic ketamine to prevent shivering in parturients undergoing Cesarean delivery during spinal anesthesia. Journal of clinical anesthesia 2013, 25(4):275-280.

145. Harmon AC, Cornelius DC, Amaral LM, Faulkner JL, Cunningham MW, Jr., Wallace K, LaMarca B: The role of inflammation in the pathology of preeclampsia. Clinical science 2016, 130(6):409-419.

146. Rutherford JM, Moody A, Crawshaw S, Rubin PC: Magnetic resonance spectroscopy in pre-eclampsia: evidence of cerebral ischaemia. BJOG 2003, 110(4):416-423.

147. Chudnofsky CR, Weber JE, Stoyanoff PJ, Colone PD, Wilkerson MD, Hallinen DL, Jaggi FM, Boczar ME, Perry MA: A combination of midazolam and ketamine for procedural sedation and analgesia in adult emergency department patients. Academic emergency medicine 2000, 7(3):228-235.

148. Rucci FS, Caroli G: Letter: Ketamine and eclampsia. British journal of anaesthesia 1974, 46(7):546.

149. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB, Jr., Charney DS: Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Archives of general psychiatry 1994, 51(3):199-214.

150. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH: Antidepressant effects of ketamine in depressed patients. Biological psychiatry 2000, 47(4):351-354.

151. Areias ME, Kumar R, Barros H, Figueiredo E: Comparative incidence of depression in women and men, during pregnancy and after childbirth. Validation of the Edinburgh Postnatal Depression Scale in Portuguese mothers. The British journal of psychiatry 1996, 169(1):30-35.

152. Hiltunen P, Raudaskoski T, Ebeling H, Moilanen I: Does pain relief during delivery decrease the risk of postnatal depression? Acta obstetricia et gynecologica Scandinavica 2004, 83(3):257-261.

153. Ding T, Wang DX, Qu Y, Chen Q, Zhu SN: Epidural labor analgesia is associated with a decreased risk of postpartum depression: a prospective cohort study. Anesthesia and analgesia 2014, 119(2):383-392.

154. Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Alkondon M, Yuan P, Pribut HJ, Singh NS et al: NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 2016, 533(7604):481-486.