



## Ketamine: An Update for Obstetric Anesthesia

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### 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 cardiopulmonary 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<sup>2+</sup>) 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  $\leq 20 \mu\text{g/kg/min}$  [24,25]. Previous studies have indicated that ketamine plasma concentrations at 0.15  $\mu\text{g/ml}$  and 0.04  $\mu\text{g/ml}$  following 0.5 mg/kg of i.m. or oral administration produced significant analgesic effect. These concentrations were much lower than awakening plasma concentrations of 0.64 -1.12  $\mu\text{g/ml}$  [26]. Except for preventing  $\text{Ca}^{2+}$  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  $\mu$ - and  $\delta$ -opioid receptors were related to ketamine analgesia [30]. However, ketamine analgesia did not seem to be the result from interaction with opioid receptors 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  $\alpha$  (TNF- $\alpha$ ), Interleukin 6 (IL-6), and IL-8 levels as well as stabilization of neutrophil activation and suppressed NF- $\kappa\text{B}$  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 beneficial to asthmatic parturients due to its bronchodilatory 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 delirium, 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. administered slowly over at least one minute 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  $2.6 \pm 2.2$   $\mu\text{g/mL}$  to  $5.5 \pm 3.8$   $\mu\text{g/mL}$  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 GABA<sub>A</sub> 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 epileptic 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 differentiate 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 depress 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  $\geq 2$  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 Incision 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 neurotoxicity 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 neurotoxic 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 jeopardizing 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. Remifentanyl 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 remifentanyl 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 obstetric 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  $0.588 \pm 0.208$  µg/ml in epidural group and  $1.925 \pm 0.149$  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 ( $102.95 \pm 20.10$  mins) was longer compared with i.v. injection ( $62.54 \pm 14.93$  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 local 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 vomiting, 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 abruptio 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 dexmedetomidine [139]. However, with significant increased blood volume and cardiac workload during pregnancy, any further minor increase of catecholamines could aggravate cardiac burden, and lead to heart failure and some other deteriorious 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 vomiting could be induced by injection of catecholamines into lateral ventricle in the brain [142]. Ketamine may induce nausea and vomiting 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 antiemetic 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- $\alpha$ , 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- $\alpha$ , 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. Furthermore, 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  $\leq 1.5$  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 remifentanyl, 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 anesthetics 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" concentration 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.

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