Journal of Experimental and Basic Medical Sciences 2022;3(1):22-25

Review

Ketamine-Induced Bladder Dysfunction

Ayşe Yürekli[1], Oytun Erbaş[1]

ABSTRACT

Ketamine is used to induce and maintain anesthesia prior to surgery. It was approved by the Food and Drug Administration in 1970 for the use of anesthetic and analgesic drugs, and patients who will be subjected to anesthesia receive intramuscular and intravenous administration. Ketamine has recently been shown to be effective in treating severe depression and has been used as an antidepressant, particularly in individuals with suicidal tendencies. It has been observed that suicidal individuals withdraw from this idea within a short period of time with ketamine treatment and approach the treatment positively. Ketamine blocks the sensory input in the brain, severing communication between the body and the brain. It is also used for malicious purposes, such as drugs, due to its perceptual delusion. The most common side effects of ketamine include hypertension, anorexia, nausea, respiratory depression, and lower urinary tract symptoms. It is excreted from the body by 96% of urine. For this reason, the most serious adverse effect is on the lower urinary system. In ketamine addicts, bladder wall thickening and related renal diseases could have serious consequences. In this review, ketamine and its effects on the bladder were examined.

Keywords: Bladder, ketamine, lower urinary tract symptoms, renal toxicity, side effects

Ketamine (RS-2-[2-chlorophenyl]-2-[methylamino] cyclohexanone) is a dissociative anesthetic used for anesthesia, pain management, and treatment-resistant depression (TRD), and suicidality worldwide.[1] It produces profound analgesia and amnesia. This drug was approved as an anesthesia medication by the Food and Drug Administration in the 1970s. As studies continued, anti-inflammatory and antidepressant properties of ketamine were also observed.[2,3] The first study on the antidepressant properties of ketamine was published in 2000.[4] Due to its effectiveness, it has been a potent antidepressant, particularly in subjects who had previously failed other antidepressant treatments. With its use in the treatment of neuropathic pain and depression, an effective improvement has been observed in suicidal patients.[5] The pharmacokinetics of ketamine include its rapid and extensive metabolism to the metabolites norketamine, dehydronorketamine, hydroxyketamine, and hydroxynorketamine.[6,7] This variety was caused by chemical branching. Norketamine is the most effective metabolite, accounting for one-third of the impact. Ketamine is soluble in water and its chemical formula is $C_{13}H_{16}CINO$.[8] It is a racemic combination of R- and S-enantiomers.[9] The active form is S+ ketamine, while the passive form is R- ketamine. S+ isomer demethylation is more potent than R- demethylation.[3,10] Dehydronorketamine concentrations in individuals with renal failure were shown to be 20% higher than in healthy people. This result has been determined that it has little effect on blood circulation.[10] Ketamine is also used as a narcotic drug worldwide. However, this contrasts with its ability to treat substance use disorders.[11] This symptom, which presents itself within 24 hours after beginning the medicine, irritates the urinary system and causes severe pain.[12] Lower urinary tract symptoms (LUTS) refer to general diseases that affect the urinary tract. Complaints affecting the quality of life, such as urinary incontinence and the sensation of frequent urinating, are reported in these patients. If the proper measures are not taken, injury to the

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey

Correspondence: Ayşe Yürekli. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

E-mail: ayseyurekli3344@gmail.com

Cite this article as: Yürekli A, Erbaş O. Ketamine-Induced Bladder Dysfunction. JEB Med Sci 2022;3(1):22-25.

doi: 10.5606/jebms.2022.1004

Received : January 23, 2022
Accepted : January 25, 2022
Published online : June 13, 2022

bladder wall can result in acute infections as well as serious consequences such as bladder cancer.[13]

KETAMINE AND NEUROTOXICITY

Ketamine is an N-methyl D-aspartate (NMDA) receptor antagonist.[14] The NMDA receptor is an ion channel that plays a significant role in many neurological and psychological processes. It is a subtype of the glutamate receptor and is especially secreted in infants' and children's developing brains. It also has a stimulating effect on neurons.[15-18] Ketamine inhibits NMDA receptors and drives developing brain cells to apoptosis. The occurrence of situations such as neuronal differentiation, dendritic development, dysphasia, and cell proliferation is referred to as neurotoxicity. In more severe cases, seizures, cerebral edema, coma, and motor weakness are observed.[19] The brains of developing rats grew as a result of ketamine administration to experimental animals. In this case, changes in the behavior of rats such as neurocognitive deficits, memory impairment, and learning difficulties were observed. Studies have confirmed that suppression of the NMDA receptor by ketamine causes this condition.[18,20] Neurological disorders caused by ketamine have become a public health issue as surgical treatments have spread.[21]

KETAMINE: USE IN ANESTHESIA

At low doses, ketamine provides analgesia (pain alleviation), antipyretic effects, and perception difficulties, but at higher doses, it completely disrupts the perception process and causes loss of response. The disruption of the perception is associated with the suppression of NMDA receptors in the brain.[22] Ketamine contains asymmetric carbon atoms. It is responsible for the formation of two isomers. These isomers, known as S+ketamine and R-ketamine, cause dosage variations when used as anesthetics. In cases where S+ ketamine is administered, a half dosage is given since it is more effective than R- ketamine. Ketamine can be administered intravenously (IV) or intramuscularly (IM).[23] Ketamine's anesthetic effects have been studied in animal experiments, and it has been found to be a safe anesthetic medication. Furthermore, the drug's rapid onset and the ability to sustain the anesthetic effect during the procedure are both advantageous in terms of usage.[24,25]

KETAMINE AND DEPRESSION

According to World Health Organization data from 2017, more than 300 million individuals globally are struggling with depression. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are used to treat depression.[26] Patients, however, develop resistance to such medications over time.[27] Moreover, such medications have been shown to be ineffective in preventing suicidal thoughts in persons who are suffering from severe depression. Ketamine has recently become popular due to its favorable benefits for people suffering from severe depression.[28] It was developed as a derivative of the medication phenylcyclohexylamine. It has been used frequently, especially with its analgesic and anesthetic effects. While ketamine usage is still prevalent, its consequences on neurological disorders have been reported. Ketamine, a very efficient and potent antidepressant, has a complex structure. It has existed two isomers, the S+ and R- enantiomers.[29] R- ketamine is less therapeutic than S+ ketamine. While S+ ketamine has a lower effect on distraction and primary memory, its analgesic and anesthetic properties are twice as effective.[30] Side effects such as insensitivity, hallucinations, and psychotic responses were reported in patients administered S+ ketamine but not in those given the same dosage of R-ketamine. According to a study, S+ ketamine induces glucose intake in the brain, but R-ketamine inhibits glucose consumption, and it is expected to suppress the negative effects of R-ketamine.[31] Ketamine's antidepressant action is thought to be due to its suppression of NMDA receptors. In a mice depression model, NMDA antagonist suppression provided positive results.[32] A pharmaceutical company produced the S+ ketamine nasal spray for the treatment of depression; this spray quickly shows its efficacy in treatment-resistant patients and was approved in Europe.[28,33]

Anxiety, agitation, hallucinations, panic, and a peculiar feeling are the most common psychiatric adverse effects of ketamine. Increased blood pressure, headache, dizziness, nausea, and renal toxicity are some of the other side effects. These effects are quickly reversed.[33]

KETAMINE AND BLADDER

For its accessibility and low cost, ketamine is widely used for recreational reasons, particularly in Asian countries. However, side effects are a major problem. In addition to its psychological side effects, severe urinary system diseases have been identified. Most ketamine addicts struggle with ketamine-induced ulcerative cystitis (KIC). KIC exhibits symptoms such as

bloody urine, burning when urinating, and frequent urination. Ketamine-induced KIC develops, resulting in fibrotic alterations in the bladder, reduced capacity due to bladder wall thickening, and increased urine frequency.[34] The stress of mitochondrial and endoplasmic reticulum pathways caused by ketamine use has been proven in animal studies to be efficient in bladder cell apoptosis. Histological studies of the bladders of mice given ketamine revealed significant histopathological alterations.[35] More than 20% of recreational ketamine users had severe LUTS. It is suspected that ketamine causes a chemical irritation of the urothelium. Long-term usage causes a decrease in bladder capacity due to hydronephrosis. This condition can also cause various renal problems. Studies on this issue should be considered by health professionals, and it's important to pay attention to whether LUTS occurs in individuals who use ketamine for depression treatment.[36]

In conclusion, when the effects of ketamine on patients with severe depression are researched, it is shown that ketamine is particularly helpful for suicidal depression patients. The glutamate receptor NMDA in the brain is suppressed by ketamine. Glutamates are neurotransmitters in our brain and allow nerves to communicate with one another, whereas ketamine blocks this communication. The person whose brain-body relationship is blocked enters a trance condition. This is exactly how ketamine's anesthetic effect works. Ketamine is supposed to inhibit suicide ideas in the brains of severely depressed people. Overdosing on the drug ketamine, which is popular among young people, especially in low-income countries, can lead to death. It has a significant adverse effect of thickening the bladder wall. This thickening can cause significant renal injury and renal failure. Although the exact mechanism is unknown, ketamine should be used with caution to avoid negative consequences.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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