Section: Psychiatry

Original Research Article

EVALUATION OF KETAMINE MASKED BY SURGICAL ANESTHESIA IN PATIENTS WITH DEPRESSION: AN INSTITUTIONAL BASED STUDY

Received : 05/05/2024
Received in revised form : 20/05/2024
Accepted : 10/06/2024

Keywords:
Depression, Ketamine.

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DOI: 10.47009/jamp.2024.6.3.107

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (3); 522-524

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Abstract

Background: This study was conducted to assess ketamine masked by surgical anesthesia in patients with depression.

Materials and Methods: Adults undergoing non-cardiac, non-intracranial elective surgery were the target population. Participants who underwent perioperative mental health screening were given the 8-item Patient Health Questionnaire (PHQ-8). A diagnosis of major depressive disorder (MDD) (single or recurring), and a major depressive episode lasting at least four weeks before to screening were all inclusion criteria. With ten items measuring an individual's depression severity and a total score ranging from 0 to 60, the MADRS is a clinical rating scale that is frequently used in antidepressant trials. Higher scores correspond to more severe depression. The MADRS was administered by qualified clinical research staff members. **Results**: In this study, there were 100 subjects, out of which 56 were males and 44 were females. The mean PHQ-8 total score was 11.2±1.9 and MADRS total score was 23.4±8.5 in the subjects receiving ketamine. **Conclusion**: The mean PHQ-8 total score was less than MADRS total score among subjects receiving ketamine for depression.

INTRODUCTION

Ketamine is in clinical use since 1970. It is a unique intravenous (IV) anesthetic that produces a wide spectrum of pharmacological effects including sedation, catalepsy, somatic analgesia, bronchodilation, and sympathetic nervous system stimulation.[1,2] The availability of newer drugs, the disturbing emergence reactions of ketamine, its stigma as a "vet medicine" and gaining popularity as a drug with abuse potential are factors, which would discourage its use by present day anesthesiologists. However, ketamine because of its unique properties and newly found clinical properties has stood the test of time. It has a wide range of clinical applications even today.[3,4] Ketamine is a dissociative anaesthetic with a relatively wide safety margin and is typically used in adult and paediatric procedures as well as veterinary procedures. Structurally, it is related to phencyclidine (PCP) and primarily acts on the glutamatergic system as an N-methyl-D-aspartate (NMDA) antagonist. Compared to PCP, ketamine has a shorter duration of action and is associated with fewer behavioural and adverse effects.[5,6] Ketamine affects multiple neurotransmitter systems, including the opioidergic, monoaminergic, glutamatergic, and muscarinic systems, as well as substance P and sigma receptors. Early work by Skolnick and colleagues implicated the glutamatergic system in depression,[7] and research over the past three decades further implicated the NMDA receptor in modulating the molecular and cellular processes important for synaptogenesis and neuroplasticity.[8] A recent study demonstrated that blockade of NMDA-dependent burst activity in the lateral habenula (LHb) mediated antidepressant-like effects in animals,[9] and neurochemical and functional imaging studies have also corroborated that ketamine treatment partly reverses the glutamatergic and gamma aminobutyric acid (GABA)-ergic dysfunction previously identified in individuals with depression.[10] This study was conducted to assess ketamine masked by surgical anesthesia in patients with depression.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

MATERIALS AND METHODS

Adults undergoing non-cardiac, non-intracranial elective surgery were the target population. Participants who underwent perioperative mental health screening were given the 8-item Patient Health Questionnaire (PHQ-8). A diagnosis of major depressive disorder (MDD) (single or recurring), and a major depressive episode lasting at least four weeks before to screening were all inclusion criteria. The Mini International Neuropsychiatric Interview Module A14 verified the diagnosis of MDD. The same sample was evaluated one, two, and three days after infusion because participant dropout didn't happen until after day three of outcome assessment. Statistical analysis was conducted using SPSS software.

RESULTS

In this study, there were 100 subjects, out of which 56 were males and 44 were females. The mean PHQ-8 total score was 11.2±1.9 and MADRS total score was 23.4±8.5 in the subjects receiving ketamine.

Table 1: Gender-wise distribution of subjects

Gender	Number of subjects	Percentage
Males	56	56%
Females	44	44%
Total	100	100%

Table 2: Depression scores of subjects receiving ketamine

Parameter	Score
PHQ-8 total score	11.2±1.9
MADRS total score	23.4±8.5

DISCUSSION

Ketamine, a dissociative anesthetic with multiple molecular targets,[11,12] is associated with rapid-acting antidepressant effects in patients with major depressive disorder (MDD), including those with treatment-resistant depression (TRD).[13-15] Across studies, an intravenous infusion of 0.5 mg/kg ketamine produces a clinical response in 41% and remission in 19% of patients with TRD at 24 hours.[16] Therapeutic effects appear within 2 hours of a single ketamine infusion. In most randomized controlled trials (RCTs) of ketamine for depression, participant masking has been nearly impossible given the drug's obvious acute psychological effects. Inadequate masking presents a major confound to interpreting studies of ketamine, as well as other rapid-acting psychoactive therapeutics such as psilocybin and methylenedioxymethamphetamine (MDMA),[17-20] to the extent that most investigations do not report on the success of participant masking. This study was conducted to assess ketamine masked by surgical anesthesia in patients with depression.

In this study, there were 100 subjects, out of which 56 were males and 44 were females. The mean PHQ-8 total score was 11.2±1.9 and MADRS total score was 23.4±8.5 in the subjects receiving ketamine. Lii TR et al,[21] In a triple-masked, randomized, placebo-controlled trial, 40 adult patients with major depressive disorder were randomized to a single infusion of ketamine (0.5 mg/kg) or placebo (saline) during anaesthesia as usual for routine surgery. The primary outcome was depression severity measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) at 1, 2, and 3 days post-infusion. The secondary outcome was the proportion of participants with clinical response (≥50% reduction in MADRS scores) at 1, 2, and 3 days post-infusion. After all follow-up visits, participants were asked to guess which intervention they received. Mean MADRS scores did not differ between groups at screening or pre-infusion baseline. One serious adverse event occurred in each group, unrelated to ketamine administration. In adults with major depressive disorder, a single dose of intravenous ketamine delivered during surgical anaesthesia had no greater effect than placebo in acutely reducing the severity of depressive symptoms. This trial successfully masked treatment allocation in moderate-to-severely depressed patients using surgical anaesthesia. While it is impractical to use surgical anaesthesia for most placebo-controlled trials, future studies of novel antidepressants with acute psychoactive effects should make efforts to fully mask treatment assignment in order to minimize subject-expectancy bias. Dwyer JB et al,[22] conducted an active-placebo-controlled study of ketamine's safety and efficacy in adolescents. In this proof-of-concept randomized, double-blind, single-dose crossover clinical trial,[17] adolescents (ages 13-17) with a diagnosis of major depressive disorder received a single intravenous infusion of either ketamine (0.5 mg/kg over 40 minutes) or midazolam (0.045 mg/kg over 40 minutes), and the alternate compound 2 weeks later. All participants had previously tried at least one antidepressant medication and met the severity criterion of a score >40 on the Children's Depression Rating Scale-Revised. The primary outcome measure was score on the Montgomery-Åsberg Depression Rating Scale (MADRS) 24 hours after treatment. A single ketamine infusion significantly reduced depressive symptoms 24 hours

ISSN (O): 2687-5365; ISSN (P): 2753-6556

after infusion compared with midazolam. In secondary analyses, the treatment gains associated with ketamine appeared to remain 14 days after treatment, the latest time point assessed, as measured by the MADRS. A significantly greater proportion of participants experienced a response to ketamine during the first 3 days following infusion as compared with midazolam (76% and 35%, respectively). Ketamine was associated with transient, self-limited dissociative symptoms that affected participant blinding, but there were no serious adverse events.[22]

CONCLUSION

The mean PHQ-8 total score was less than MADRS total score among subjects receiving ketamine for depression.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556