# Comparison of the Effects of Haloperidol and Midazolam on Reduction of Adverse Psychotomimetic Reactions after Induction of Anesthesia with Ketamine in Adults

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**Abstract**

As an anesthetic agent, ketamine is associated with a number of adverse psychological reactions after patient recovery (Motamed et. al., 2012). Midazolam is currently used to mitigate such adverse reactions. However, they still cause discomfort in patients and sometimes their next of kin. The present study aimed to compare the effect of midazolam and haloperidol on decreasing these adverse psychological reactions.

In this clinical trial, patients who were subjected to anesthesia induction by ketamine were randomly divided into haloperidol, midazolam, and distilled water (as control) groups. All patients underwent orthopedic surgery with a maximum duration of 2 hours. After the recovery of the patients, a questionnaire was completed by the anesthesiologist. In addition to demographic data, the questionnaire included a number of questions about adverse psychological reactions such as inaudible speech, uncontrollable crying and laughter, strange feelings, illusions, anxiety, and agitation. After completing the questionnaires, the data were introduced into SPSS and analyzed with statistical tests.

A total of 60 patients including 30 men and 30 women were enrolled in the study. The mean age of the patients was 32.9±9.5 years ranging from 16 to 50 years. Twenty patients received the premedication (pre-anesthetic drug) haloperidol before the induction of anesthesia, 26 patients received midazolam, and 14patients received distilled water.

The patients were similar in terms of age, gender, and ASA group. The recovery time for midazolam and haloperidol was significantly longer than that of distilled water ($p$=0.02). In addition, the number of adverse psychological reactions were significantly higher in the midazolam ($p$=0.02)

and haloperidol ($p$=0.04) groups than in the distilled water group. However, they occurred less often in midazolam group than the haloperidol group with no significant difference.



Haloperidol can reduce the adverse psychological reactions of ketamine, but this reduction is not as prominent as midazolam.

**Keywords:** Ketamine; Adverse Psychological Reactions; Haloperidol; Midazolam.

## 1. Introduction

Ketamine is a drug particularly suited to induction of anesthesia in emergency patients. It is the only anesthetic agent that increases blood pressure, heart rate, and cardiac output (Kalisvaart et. al., 2005). Ketamine also has analgesic and sedative properties (Cole et. al., 2002). Occurrence of adverse psychological reactions is the problem with the use of this drug, which can be seen in 10% to 30% of cases, even some studies have reported them up to 100% (Atlas et. al., 2007).

Age, sex, dosage, psychological background, and associated drugs can affect the development of adverse psychological reactions after the use of ketamine anesthetic agent. These adverse reactions are more prevalent in adults, in women, and when high doses of the drug are used (Schrader et. al., 2008). People with a history of mental illness, such as those who fall into a dream alone, are more prone to adverse psychological reactions (Campbell et. al., 2009).Benzodiazepines are currently used to confront adverse psychological reactions. However, their effectiveness is still to be seen (Sherwin et. al., 2000).

The present study aimed to evaluate the effect of haloperidol on the reduction of ketamineinduced adverse psychological reactions and compare it with midazolam as a medicine used to reduce these adverse reactions.

## 2. Materials and Methods

In this randomized clinical trial, all patients aged 16-50 years who were admitted to Imam Khomeini Hospital in 2016-2017 and anesthetized with ketamine were enrolled in the study. The study was approved by the Ethics Committee of Tehran University of Medical Sciences and the consent was obtained from the patient after giving the necessary explanations.

The subjects were ASA Class I and II. The exclusion criteria were history of cardiovascular disease (hypertension, congenital or acquired cardiac diseases), history of mental illness (depression, mania, schizophrenia, *etc.*), and Parkinson's disease. The study was conducted on patients undergoing orthopedic surgery less than two hours in duration. All patients were matched in terms of age, sex, and other confounding factors (*e.g.* the history of using psychosocial drugs).

Haloperidol was used as a premedication before induction of anesthesia. The effect of this drug on reducing the incidence of adverse psychological reactions after induction of anesthesia was compared with midazolam and distilled water as the control. Ketamine was used in these patients as the anesthesia induction drug at a dose of 1-2 mg/kg of body weight.

The patients were randomly divided into three groups. Five minutes before induction of anesthesia, the first group received 3 mg intravenous haloperidol, the second group received 3 mg midazolam, and the third group received distilled water. Sufentanil was used as the analgesic drug and atracurium as the muscle relaxant in all patients.

After the end of surgery and recovery of the patient in the recovery ward, a questionnaire was filled out for each patient and the adverse psychological reactions were studied. The questionnaire was completed by a person who did not know the method of anesthesia and the premedication drug. The results were scored and then analyzed by SPSS using *t*-test.

## 3. Results

A total of 60 patients including 30 men and 30 women were enrolled in the study. The mean age of the patients was 32.9±9.5 years ranging from 16 to 50 years. Twenty patients received the



premedication (pre-anesthetic drug) haloperidol before the induction of anesthesia, 26 patients received midazolam, and 14 patients received distilled water.

There was no significant difference between age, sex, and duration of surgery in different groups.But there was a significant difference between the midazolam and distilled water groups in the duration of operation. In the midazolam group, this time (75.0±26.0) was longer than the distilled water group (55.0±41.3), which should be corrected during the study period.

In addition, there was a was significant difference in the duration of surgery between the drug groups and the distilled water group (haloperidol: 55.0±43.3).

The recovery time in the midazolam and haloperidol groups was significantly longer than the distilled water group ($p$=0.02);i.e. it was 18.5±6.0 min in the distilled water group, 31.9±17.8 min in the midazolam group, and 25.5±10.8 min in the haloperidol group.

In the recovery ward, patients were questioned and scored. The questions were about inaudible speech, uncontrollable crying and laughter, strange feelings, illusions, anxiety, and agitation. The answers were entered into the questionnaire. Each of these symptoms were scored 1 and the scores were summed. The scores were then distributed and obtained for each group and the adverse reactions were calculated as mean ± SD in order to compare the different groups (Table 1). Comparison of the groups with nonparametric *t*-test showed a significant difference between the midazolam and haloperidol groups with the distilled water group; so that the mean scores in the distilled water group (1.8±0.1) were higher than the haloperidol group (1.2□1.1) ($p$=0.04) and the midazolam group (1.08±0.9) ($p$=0.02). This mean for the haloperidol group was similar to the midazolam group ($p$>0.05).

Table 1. Comparison of mean scores of the adverse psychological reactions questionnaire in the study groups

| Group | Number | Percent | Mean ± SD |
|---|---|---|---|
| Haloperidol | 20 | 33.3% | 1.2□1.1 |
| Midazolam | 26 | 43.3% | 1.08±0.9 |
| Distilled water | 14 | 23.3% | 1.8±0.1 |
| Total | 60 | 100% | 1.3±1.0 |

## 4. Discussion

### 4.1. Increased recovery time for haloperidol and midazolam

In this study, the use of haloperidol was effective in preventing ketamine-induced adverse reactions, but this preventing effect was not as effective as midazolam.

### 4.2. Similar studies in this field

In a study in India, the effects of diazepam and haloperidol were compared in terms of reduction of ketamine-induced adverse psychological reactions, and it was concluded that diazepam is more successful than haloperidol in preventing the adverse reactions of ketamine (Krystal et. al., 1994).Another study by Haleem *et. al.* in 2016 found that haloperidol was effective in preventing ketamine-induced adverse psychological reactions (Haleem et. al., 2016). In a study by Mostafa Amr in Egypt in 2013, haloperidol was found to be effective in reducing adverse psychological reactions (Mostafa et. al., 2013). The present study revealed that haloperidol was effective in preventing

ketamine-induced adverse reactions; however, this preventative effect was not as pronounced as that of midazolam.

## 5. Conclusion

According to this study, haloperidol can be effective in preventing ketamine-induced adverse psychotomimetic reactions, and hence it is recommended that it is used before induction of anesthesia with ketamine.



## References

Amr, M. A., Shams, T., & Al-Wadani, H. (2013). Does haloperidol prophylaxis reduce ketamineinduced emergence delirium in children?. Sultan Qaboos University Medical Journal, 13(2), 256.

Atlas, G. M., & Milles, M. (2007). Haloperidol for the treatment of ketamine-induced emergence delirium. J Anaesthiol Clin Pharmacol, 23, 65-7.

Campbell, N., Boustani, M. A., Ayub, A., Fox, G. C., Munger, S. L., Ott, C., ... & Singh, R. (2009). Pharmacological management of delirium in hospitalized adults–a systematic evidence review. Journal of general internal medicine, 24(7), 848-853.

Cole, J. W., Murray, D. J., McALLISTER, J. D., & Hirshberg, G. E. (2002). Emergence behaviour in children: defining the incidence of excitement and agitation following anaesthesia. Pediatric Anesthesia, 12(5), 442-447.

Haleem,S., Hasan.M., Fatima, N., MdKashif, J. (2016). A Novel Use in Ketamine Induced, 10861088

Kalisvaart, K. J., De Jonghe, J. F., Bogaards, M. J., Vreeswijk, R., Egberts, T. C., Burger, B. J., ... & Van Gool, W. A. (2005). Haloperidol prophylaxis for elderly hip‐surgery patients at risk for delirium: a randomized placebo‐controlled study. Journal of the American Geriatrics Society, 53(10), 1658-1666.

Krystal, J. H., Karper, L. P., Seibyl, J. P., Freeman, G. K., Delaney, R., Bremner, J. D., ... & Charney, D. S. (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Archives of general psychiatry, 51(3), 199-214.

Motamed, F., Aminpour, Y., Hashemian, H., Soltani, A. E., Najafi, M., & Farahmand, F. (2012). Midazolam-ketamine combination for moderate sedation in upper GI endoscopy. Journal of pediatric gastroenterology and nutrition, 54(3), 422-426.

Postoperative Fulminant Psychosis. International Journal of Science and Research (IJSR), 5.

Schrader, S. L., Wellik, K. E., Demaerschalk, B. M., Caselli, R. J., Woodruff, B. K., & Wingerchuk, D. M. (2008). Adjunctive haloperidol prophylaxis reduces postoperative delirium severity and duration in at-risk elderly patients. The neurologist, 14(2), 134-137.

Sherwin, T. S., Green, S. M., Khan, A., Chapman, D. S., & Dannenberg, B. (2000). Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. Annals of emergency medicine, 35(3), 229-238.