ANALYSIS

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# Effect of the time interval between administering midazolam and ketamine on delirium after gynecologic surgeries: A randomized parallel clinical trial

**Hashem Jarineshin[1], Fereydoon Fekrat[2], Saeed Kashani[3], Mehrdad Malekshoar[4], Majid Vatankhah[5]☼**

***Background:*** **Ketamine as a dissociative agent can induce dreaming and hallucinations during revival, which have limited its use in adults. The co-administration of midazolam, however, has been clearly shown to attenuate the perceptual abnormalities and thought disorders induced by ketamine.** ***Objective:*** **The aim of this study was to evaluate the latency interval effect midazolam and ketamine on post-anesthetic delirium after minor gynecologic surgeries.** ***Methods:*** **A randomized parallel double blinded clinical trial. The study was conducted from September 2015 to March 2016. A total of 100 women undergoing minor gynecological surgeries were randomized into 4 groups. The median age of the patients was 31.08 ± 8.99. In this trial, the groups were defined according to the time intervals of 0, 2.5, 5, and 7.5 minutes between the administration of midazolam (0.05 mg/kg) and ketamine (1.5 mg/kg). Delirium was measured by the degree of comfort, speech impediment, and delirium level. The data were analyzed in SPSS software by chi square and t tests. Our primary endpoint was the extent of midazolam`s administration time lag effect on ketamine`s post anesthetic delirium level.** ***Results:*** **The incidence of delirium in all participants according to degree of comfort or tranquility, speech impediment, and delirium were 6%, 17%, and 22%, respectively. The comparison among groups showed no significant difference between the time interval of injections and the degree of tranquility and speech impediment, while the time interval and degree of delirium showed significant differences between group 1 and 3, group 2 and 3, and group 2 and 4. An increased time interval between administration of drugs to 5 minutes meaningfully decreased the delirium level but a latency interval of greater than or less than 5 minutes did not show any significant effects on delirium.** ***Conclusion:*** **According to our findings, it is better to administer midazolam 5 minutes before ketamine in order to effectively decrease the incidence of delirium.**

## BACKGROUND

Anesthetic sedation is used to eliminate pain, anxiety and unpleasant memories of a variety of interventions. The technique of combining midazolam/ketamine is called "dissociative sedation" and can be a suitable approach to conscious sedation. (1) Ketamine is a strong anesthetic that also has analgesic properties (2). When used at a high dose (> 0.5 mg/kg), it causes symptoms of dysphoria similar to psychosis (2). In fact, symptoms such as dreaming, hallucination, and undesirable effects such as nightmares have limited the use of ketamine in adult patients (3). Simultaneously administering midazolam has shown that it can reduce the perceptual abnormalities and thought disorders without effecting the amnesia and positive changes of mood due to ketamine (4). The cardio-respiratory impact of this combination is less than for other methods of sedation (5 & 6). In fact, it has been shown that using midazolam as an auxiliary drug improves the revival phase after anesthesia due to ketamine, and thus this combination treatment has become routine in emergency and non-emergency interventions (7) as one of the most effective and safest sedative-analgesia techniques (8). Midazolam and ketamine are administered in various ways including oral, nasal, rectal, intra-muscular and intra-venous, and they do not cause pain or phlebitis during injection (2). After searching the international and national

[1]Associate Professor of Anesthesiology, Cardiothoracic anesthesia fellowship, Anesthesiology, Critical Care and Pain Management Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran; [2]Anesthesiologist, Anesthesiology, Critical Care and Pain Management Research Center Hormozgan University of Medical Sciences, Bandar Abbas, Iran; [3]Associate Professor of Anesthesiology, Cardiothoracic anesthesia fellowship, Anesthesiology, Critical Care and Pain Management Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran; [4]Assistant Professor of Anesthesiology, Intensive Care fellowship, Anesthesiology, Critical Care and Pain Management Research Center Hormozgan University of Medical Sciences, Bandar Abbas, Iran; [5]Assistant Professor of Anesthesiology, Assistant of Intensive Care fellowship, Anesthesiology, Critical Care and Pain Management Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

☼*Corresponding Author:* Majid Vatankhah, Anesthesiology, Critical Care and Pain Management Research Center, Hormozgan University of Medical Sciences, Jomhouri Eslami Boulevard, Shahid Mohammadi Hospital, Bandar Abbas, Iran. Postal Code: 7919915519. E-mail: hormozgan91@yahoo.com

literature databases, we did not find any complete article or review article investigating the effect of the time interval between intravenous midazolam and ketamine on delirium or other side effects of ketamine. However, revealing such a latency interval effect could introduce a new method for administering midazolam and ketamine that can help anesthesiologists decrease postoperative complications and delirium.

## METHODS

This study was given ethical approval by the University of Hormozgan Medical Sciences Ethics Committee on August 25, 2015 (N◦ 3-HEC-93-8-20). The trial was registered in the Iranian Registry of Clinical Trial IRCT2016010518091N7. Written informed consent was obtained from each patient prior to the intervention in accordance with the Helsinki Declaration. The study interventions and possible side effects were explained to the patients. In this double blind randomized parallel clinical trial, 124 female patients (16–50 years old) with ASA I–II were recruited from those who were admitted to the Obstetrics and Gynecological Department of Dr. Ali Shariati Bandar Abbas hospital for minor surgical procedures (operation duration was expected to be less than 20 minutes). Exclusion criteria were an allergy to the study drugs; addiction to drugs or psychotropic substances; an ASA greater than II; a history of hypertension, psychiatric or neurological disorders; and a body mass index of over 30 or under 18. After the patients entered the operating room, standard monitoring including ECG, pulse oximeter, and NIBP were applied and baseline vital signs were recorded. The patients were allocated by block randomization (1:1) into 4 groups regarding the time interval between intravenous midazolam (0.05 mg/kg) and ketamine (1.5 mg/kg). The block randomization was produced by a computer software program that had defined 14 blocks with 8 in each block. Midazolam was administered at the following time points: 0, 2.5, 5, and 7.5 minutes before ketamine in groups 1 to 4, respectively. Each time interval group was identified by predetermined codes and were applied by the anesthesia resident. The demographic variables of the patients, number of previous anesthetics, type of surgery, overall dosage of midazolam and ketamine used, and time period of surgery from induction of anesthesia to transfer of the patient to the recovery room were recorded in the check list. The patients were kept in a shared recovery area. After awakening and complying with the instructions, patients were examined as shown in Table 1 (9) until discharge from the recovery room and those who had a delirium scale ≥ 3 were defined as patients with delirium and were treated with haloperidol. The researcher who was recording the intensity of delirium in the recovery room was blinded to the patient's time interval group and the random allocations were applied by the anesthesiologists in charge of conducting the initial phases of induction and maintenance of the anesthesia. The recovery personnel were also instructed to report any side effects without knowing which group the patient was allocated to.

### Statistical analysis

The primary outcome was delirium after ketamine administration. In order to calculate the required sample size, a pilot study was conducted with 20 women. The formula shown in Figure 1 was used to calculate the groups. The type I error (α) value was taken as 0.05 and the β value was assumed as 80% power for analysis. The $p_i$ is the proportion value in the group I and $p_j$ is the proportion value in the group j, $\varepsilon_{ij}$ is the difference of proportions in the related groups, τ is the number of possible comparisons made, $n_{ij}$ is the total number of samples according to the proportion of i and j groups, and n is the total number of samples needed for the maximum numbers of double comparisons.

$$n_{ij} = \frac{\left(Z_{\frac{\alpha}{2\tau}} + Z_{\beta}\right)^2 . \left[p_i(1-p_j) + p_j(1-p_j)\right]}{\varepsilon_{ij}^2}$$

Number of comparisons =τ

$\varepsilon_{ij} = p_i - p_j$

n = max {$n_{ij}$: all interested pairs}

**Figure 1** Formula for calculating the number of samples for the groups needed

The percentage of women in the pilot study who had delirium in the zero minute groups was 0.36%, 2.5minute group 0.6%, 5minute group 0%, and 7.5 minute group 0.15%. The numbers of samples for each double comparison were extracted (Table 1) and the highest number was considered (100), and accordingly each group must have 25 patients. A possible drop out of 10% was considered and therefore 28 patients were needed for each group. A total number of 124 patients were recruited and a final number of 25 women were analyzed in each group (Figure 2). After commencement of the trial, patients' that required rescue anesthetic agents either for inadequate anesthesia level, surgical reasons, or airway management were excluded from analysis. All statistical analyses were performed using SPSS software (SPSS version 16, SPSS Inc., Chicago, USA.). Results are reported as mean ± standard deviation (SD) for the quantitative variables and categorical variable rate. The groups were compared using Student's t-test, chi-square, and one-way ANOVA methods, and a P value <0.05 was considered significant. The trial recruitment was started on 10/1/2016 and ended on 19/2/2016 as the number of patients analyzed reached the required number.

## RESULTS

A total of 100 women candidates for minor gynecologic surgeries were included in this study. The average age of the participants was 31.08 ± 8.99 years (range 17–50 years) among whom 88% were below 45 years old. The average duration of anesthesia was 12.41 ± 3.63 min (range 5–20 min) and 45% of the patients were unconscious for over 12 min. Overall, the four groups were similar regarding age, height, weight, average surgery time, ketamine and midazolam usage (Table 2).

About 68% of the patients had experienced a previous anesthesia, but there was no significant difference between the study groups in this aspect. The types of surgeries were D&C (91%), loop electrosurgical excision procedure (LEEP) (5%), re-stitching of a wound (1%), hymenotomy (1%), and removal of an IUD (2%). No significant difference was observed in the types of surgery conducted between the groups (Figure 3).

Among all patients during the recovery period the following results were obtained. According to the tranquility rating: 44% (44) of participating patients were very tranquil, 50% (50) were tranquil, 5% (5) were restless, and 0% (0) were very restless and 1% (1) were severely restless. Based on the degree of tranquility criterion, 6% had delirium. According to the speech rating: 13% (13) were completely silent, 70% (70) were quiet, 15% (15) lightly spoke and 1% (1) spoke quite a lot and 1% (1) spoke and cried at the same time. Based on the degree of speech impediment criterion, 17% of patients had delirium. According to the delirium rating: 31% (31) clearly had no delirium, 47% (47) did not have delirium and 20% had probably experienced delirium. One had clearly

**Table 1** Criterion for assessing degree of tranquility, speech and delirium

| | Rating tranquility | Rating speech | Rating delirium |
|---|---|---|---|
| Degree | | | |
| 1 | **Very tranquil**: sedentary even with provocation | **Very quite**: no speech even with provocation | **Definitely has not**: asleep |
| 2 | **Tranquil**: slight mobility (up to 2 movements a minute) without provocation | **Quite**: responsive to provocation | **Has not**: open eyes and communicates with surroundings |
| 3 | **Restless**: up to 4 movements a minute | **Little speech**: spontaneous speech every 5mins. | **Probable**: sometimes shows vague and aimless movements |
| 4 | **Very restless**: over 4 movements in a minute | **Talkative**: not quite for 1 min. | **Has**: offensive motions |
| 5 | **Severely restless**: in one minute, not restful for 30secs. | **Talkativeness with crying:** Any episode | **Severe**: severely offensive motions accompanied with catheter removal |

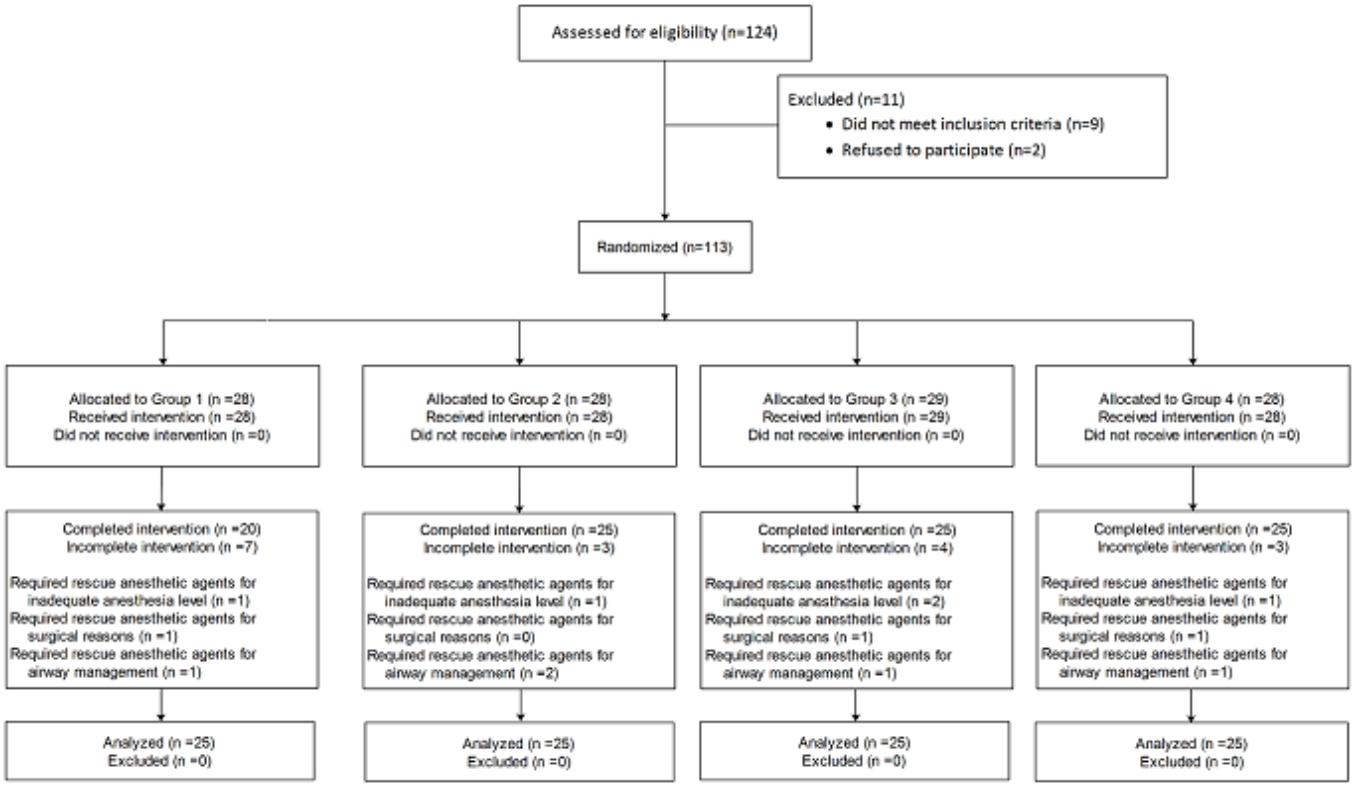
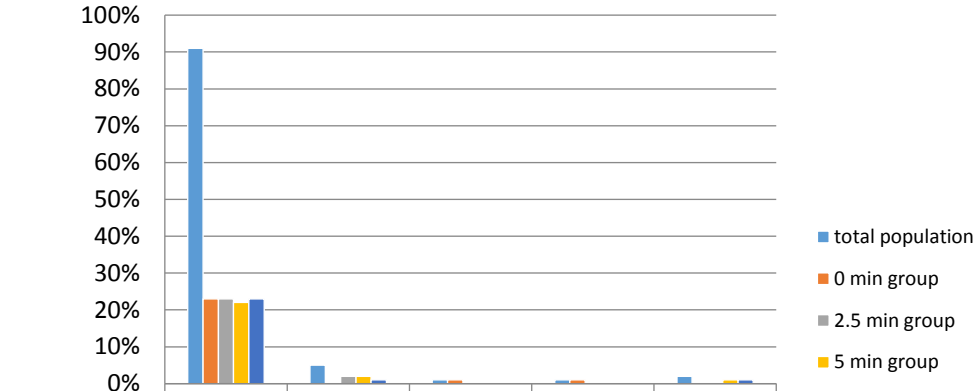



**Figure 2** Consort diagram

**Table 2** Demographic results and their comparison in four groups. (Mean ± Standard Deviation)

| | Total | Group1 | Group2 | Group3 | Group4 | P- value |
|---|---|---|---|---|---|---|
| Age (yr) | 31.08±8.99 | 29.92±9.82 | 29.56±7.78 | 33.44±10.66 | 31.40±7.26 | 0.145 |
| Heigh(cm) | 162.13±6.7 | 161.72±5.24 | 161.64±6.08 | 163.52±7.49 | 161.64±5.81 | 0.645 |
| Weight (Kg) | 62.07±12.52 | 61.64±9.58 | 59.64±8.99 | 60.84±13.45 | 66.16±16.36 | 0.277 |
| Surgerytime (min) | 12.41±3.63 | 11.40±4.07 | 12.56±2.84 | 13.56±3.63 | 12.12±3.75 | 0.201 |
| Ketaminedosage (mg) | 82.35±22.36 | 82.2±24.58 | 85±15.67 | 78.20±25.77 | 84±22.82 | 0.099 |
| Midazolam Dosage (mg) | 3.14±0.64 | 3.22±0.64 | 2.94±0.56 | 3.04±0.61 | 2.34±0.71 | 0.723 |




| Type of surgery | D&C: dilatation and curettage | LEEP: Loop Electrosurgical Excision Procedure | RSOW: re-stitching of wound | HYME: hymenotomy | IUDR: removal of IUD |
|---|---|---|---|---|---|
| total population | 91% | 5% | 1% | 1% | 2% |
| 0 min group | 23% | 0% | 1% | 1% | 0% |
| 2.5 min group | 23% | 2% | 0% | 0% | 0% |
| 5 min group | 22% | 2% | 0% | 0% | 1% |
| 7.5 min group | 23% | 1% | 0% | 0% | 1% |

**Figure 3** Types of surgery among the study groups

**Table 3** Frequency and percentage of each delirium criteria in four groups and total population

| | | 0 min | 2.5 min | 5 min | 7.5 min | Total |
|---|---|---|---|---|---|---|
| Degree of tranquility | Highly tranquil | 11 (%11) | 14(%14) | 11(%11) | 8(%8) | 44 (%44) |
| | Tranquil | 11 (%11) | 9(%9) | 14(%14) | 16(%16) | 50 (%50) |
| | Restless | 2 (%2) | 2(%2) | 0 | 1(%1) | 5 (%5) |
| | Highly restless | 0 | 0 | 0 | 0 | 0 |
| | Severely restless | 1 (%1) | 0 | 0 | 0 | 1 (%1) |
| | Total | 25 (%25) | 25(%25) | 25(%25) | 25(%25) | 100 |
| Degree of speech | Very quite | 1 (%1) | 2(%2) | 5(%5) | 5(%5) | 13 (%13) |
| | Quite | 19 (%19) | 18(%18) | 15(%15) | 18(%18) | 70 (%70) |
| | Slightly talkative | 3 (%3) | 5(%5) | 5(%5) | 2(%2) | 15(%15) |
| | Highly talkative | 1 (%1) | 0 | 0 | 0 | 1(%1) |
| | Highly Talkative and crying | 1 (%1) | 0 | 0 | 0 | 1(%1) |
| | Total | 25 (25%) | 25(25%) | 25(20%) | 25(25%) | 100 |
| Degree of delirium | Definitely not delirium | 6(6%) | 4(4%) | 9(9%) | 12(12%) | 31(31%) |
| | None | 11(11%) | 9(9%) | 16(16%) | 11(11%) | 47(47%) |
| | Possibly has delirium | 7(7%) | 11(11%) | 0 | 2(%) | 20(20%) |
| | Delirium | 0 | 1(1%) | 0 | 0 | 1(1%) |
| | Sever delirium | 1(1%) | 0 | 0 | 0 | 1(1%) |
| | Total | 25(25%) | 25(25%) | 25(25%) | 25(25%) | 100 |

**Table 4** Results of Chi test score to compare time intervals of injections with delirium criterion according to groups

| | Degree of tranquility | Degree of speech | Degree of delirium |
|---|---|---|---|
| | P-value | | |
| Groups 1 & 2 | 0.668 | 0.581 | 0.480 |
| Groups 1 & 3 | 0.339 | 0.238 | 0.023 |
| Groups 1 & 4 | 0.435 | 0.298 | 0.123 |
| Groups 2 & 3 | 0.178 | 0.459 | 0.001 |
| Groups 2 & 4 | 0.140 | 0.276 | 0.010 |
| Groups 3 & 4 | 0.448 | 0.459 | 0.187 |

experienced delirium and another had severe delirium. Based on the degree of delirium criterion, 22% of patients had delirium (Table 3).

In group 1 (zero minutes), 44% (11) of patients were very tranquil, 44% (11) were tranquil, 76% (19) quiet, 28% (7) probably experienced delirium and 4% (1) experienced severe delirium. In group 2 (2 ½ minutes) 56% (14) patients were very tranquil, 72% (18) were quiet, 44% (11) probably suffered some delirium, and 4% (1) patient had experienced delirium but no severe case was reported. In group 3 (3 ½ minutes) 56% (14) were tranquil, 20% (5) were very quiet, 60% (15) were quiet and 20% (5) patients had slightly spoken and no cases of probable delirium or any delirium were reported. In group 4 (7 ½ minutes) 32% (8) were very tranquil, 64% (16) were tranquil, 20% (5) were very quite 72% (18) were quiet and only 8% (2) had probably experienced delirium but no severe cases of delirium were reported (Table 3).Comparing the intervals between injection of midazolam and ketamine with the delirium assessment criterion (degree of tranquility,

speech impediment, and delirium) showed no significant difference between groups 1 & 2, groups 1 & 4, and groups 3 & 4. There were no significant differences related to speech impediment and tranquility, but there was a significant difference in intervals between injections with delirium between groups 1 & 3, groups 2 & 3, and groups 2 & 4 (P = 0.023, P = 0.001, and P = 0.01 respectively) (Table 4).

## DISCUSSION

Analgesia and sedation is an appropriate method to safely eliminate pain, anxiety, and unpleasant memories related to various types of interventions. The technique of combining midazolam with ketamine is called dissociative sedation and it can replace traditional methods of general anesthesia or conscious sedation (1). Ketamine is a potent anesthetic agent that has analgesic properties (2). When used alone at higher doses (> 0.5 mg/kg) it can cause dysphoric symptoms similar to psychosis (2). In fact, ketamine causes dreaming, hallucinations, and undesirable effects like nightmares, which has limited its use in adults (3). Simultaneous administration of midazolam has been shown to diminish the perceptual abnormalities and thought disorders without affecting amnesia and positive moods (4). In fact, midazolam is an adjunct agent that can improve the recovery of conditions caused by ketamine; in other words, this combination is currently accepted as the most effective and safest sedation analgesia technique (8). An anxiolytic and mild tranquilizing dose of intravenous midazolam is 0.015–0.03 mg/kg, which can be repeated every 30–60 minutes. The time of onset and duration of effect is related to its lipid solubility and plasma concentration, which usually peaks at 2–3 minutes after administration (10). Benzodiazepines act on the gamma-aminobutyric acid (GABA) A receptor. The alpha 1 sub unit is responsible for eliciting its tranquility, anterograde amnesia, and anti-epileptic effects and its anti-anxiety and muscle relaxing effects are mediated through the alpha 2 subunit. The drug effect is related to its plasma concentration effect since when 20% of the receptors are occupied by the benzodiazepine agent the anxiolytic effect occurs and with 60% occupation, tranquility effects are elicited (10).An important fact to know about this type of co-administration is that midazolam and ketamine have similar half-lives (11). It can be concluded that the time latency between midazolam and ketamine administration can be effective in attenuating the delirium effect and other side effects of ketamine in the context of short gynecological operations. In our literature research we did not find any studies that considered the time latency effect when co-administering midazolam and ketamine. In a study by Sener et al., 8% of the patients in the midazolam group showed restlessness (12) compared to our study where there was an overall 5% restless and 1% very restless. In contrast to our findings, Sherwin et al. stated that midazolam did not have any effect on the restlessness of children during recovery from ketamine anesthesia (7). Wathen et al. reported an increase in agitation with midazolam-ketamine compared to ketamine alone (35.7% vs. 5.7%) in the recovery of children over 10 years of age, showing a contradictory result to the present study (13). Morse et al. reported that the midazolam-ketamine combination was without any adverse events, such as unpleasant dreams or dysphoric or emergent reactions; additionally, they stated that the combination resulted in cardio-respiratory stability and can be a substitute for conventional analgesic regimes (1). The only report that evaluated the degree of talkativeness was by Chudnofsky et al., whose findings were comparable to the present study results, since they reported 13% were very quiet, 70% quiet, 15% little speech impediment, 1% talkative and 1% talkativeness with crying (14). However, in our study there were no significant differences in the degree of talkativeness and tranquility between any of the four groups, but the degree of delirium per se was considerably significantly different between group 1 vs. 3, group 2 vs. 3, and group 2 vs. 4; delirium was most frequently seen in group two and least seen in group three. Collectively, this can be interpreted to mean a 5 minute time lapse between administering midazolam and ketamine can significantly reduce the delirium related to ketamine, but a time point under or over the 5 minute interval had no significant effect on preventing this adverse outcome. In conclusion, according to our findings, administering midazolam 5 minutes before ketamine most effectively decreases the incidence of delirium.

### Recommendations

Considering that this study can be a *de novo* guideline for the use of ketamine in minor surgeries, further similar studies with a larger number of patients could be very useful, including different techniques and types of surgeries separately in order to evaluate the conditions of anesthesia and also the general usage of quantitative methods of assessment for measuring levels of delirium.

### Limitations

This study is probably the first of its kind, investigating the effect of the time latency between midazolam-ketamine injections on ketamine induced delirium; thus, there are no similar previous studies to compare it to. Also, the study groups were not very large, and additional parallel quantitative methods for evaluating the delirium level may be necessary; and finally, these results may be a matter of further debate.

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