# $ED_{50}$ for intravenous midazolam-induced amnesia and its duration in surgical patients

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## $ED_{50}$ for intravenous midazolam-induced amnesia and its duration in surgical patients

BACKGROUND: *Intraoperative awareness is a serious adverse event under general anesthesia. Midazolam has a good anterograde amnesia-inducing effect, can prevent and reduce the occurrence of intraoperative awareness. However, if the dosage of midazolam is improperly controlled, it may not produce forgetting effect, or bring obvious adverse side effects, such as respiratory depression, and delay of recovery. However, the half maximal effective dose ($ED_{50}$) of midazolam for amnesia, the duration of amnesia and the factors affecting the duration of amnesia are still inconclusive. Therefore, it is of great clinical significance to observe and determine the dose, duration and influencing factors of amnesia induced by midazolam*

METHODS: *A total of 106 patients who underwent ASA grades I-II elective operation under spinal-epidural anesthesia were intravenously injected with different doses of midazolam at 10 minutes after spinal-epidural anesthesia, every 5 minutes, the patient was presented with pictures or sounds as memory content, and heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), blood oxygen saturation ($SpO_2$), bispectral index (BIS), OAA/S and adverse events were recorded. The patient's forgetfulness was followed up in the early morning after operation.*

RESULTS: *$ED_{50}$ (the dose for amnesia in half of the subjects) was 0.031 mg/kg (95% CI: 0.027-0.036 mg/kg); $ED_{95}$ (the dose for amnesia in 95% of the subjects) was 0.044 mg/kg (95% CI: 0.038-0.071 mg/kg). After the patients were injected intravenously with 0.04 mg/kg of midazolam, the respiratory and circulatory systems were basically stable, no serious adverse events occurred, and the forgetting rate was 88.5%. ET50 (the time for half of the subjects in a state of forgetfulness) was 23.77 minutes (95% CI: 20.18-27.07 min), and the corresponding BIS was 83.22; ET05 (the time for 5% of the subjects in a state of forgetfulness) was 53.90 minutes (95% CI: 48.54-61.47 min) and the corresponding BIS was 91.38. The amnesia-inducing effect of midazolam was correlated to sedation grade, BIS and age, and was not correlated to visual memory or auditory memory.*

CONCLUSION: *In this study, the $ED_{50}$, $ED_{95}$ and maintenance time of the forgetting effect of intravenous midazolam were preliminarily determined.*

KEY WORDS: Amnesia, Duration of amnesia, $ED_{50}$, Midazolam

## Introduction

Patients under general anesthesia do not always remain unconscious during surgery. The incidence of intraoperative awareness in patients undergoing general anesthesia is 0.1–0.2% in literature. In China, this is approximatley 0.41%, which is 2-3 times higher than that cited widely in Western countries. Intraoperative awareness remains as a major concern for anesthesiologists [1].

Amnesia is the absence of recall. Benzodiazepines greatly impair the ability to learn new information, which is a condition known as anterograde amnesia. Some randomized clinical trials have reported reduced recall in surgical patients prophylactically administered with midazolamy [2].

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An inappropriate dose of midazolam will fail to produce amnesia or may cause side effects, such as respiratory depression and delayed emergence from anesthesia. No studies have reported on the median effective dose ($ED_{50}$) and maintenance time of midazolam-induced amnesia. It is of clinical importance to observe and determine the effective dose, maintenance time and factors that can influence intravenous midazolam-induced amnesia.

## Methods

### Test 1

### *$ED_{50}$ for intravenous midazolam-induced amnesia in surgical patients*

Following the Hospital Research and Ethics Committee approval, all patients signed an informed consent document explaining the research protocol. The present study was supported by Beijing Chaoyang Hospital, which included patients between March 2011 and November 2011. Patients with a history of mental or neurological disease, history of taking psychoactive or sedative-hypnotic drugs, apparent disorders of the cardiovascular or respiratory system, or liver or renal dysfunctions were excluded. None of the patients had contraindications to premedication or intraspinal anesthesia. All patients had normal binaural listening, vision and verbal exposition. Furthermore, all patients completed their elementary education or had a higher degree. No intravenous auxiliary analgesia was used during and after the operation.

### *Preliminary test*

A total of 49 ASA I–II patients (18-65 years old) received a selective operation in the lower limb or lower abdomen under combined spinal epidural anesthesia (CSEA). The operation included high ligation and stripping of the varicose great saphenous vein, high ligation of the varicocele, transurethral resection of the prostate (TUR-P) or bladder tumor (TUR-BT), knee arthroscopy, knee arthroplasty, or removal of internal fixation after surgery to repair a lower-limb fracture.

The dose range was analyzed using the Bliss method. Three patients from each group were dosed with 0.04 mg/kg (see official test below). If two patients exhibited d amnesia, the dose was up- or down-regulated by 1.5 times and 0.5 times, accordingly. All three patients exhibited amnesia under 0.06 mg/kg. Hence, this was selected as the maximum dose ($D_m$). None of the patients exhibited amnesia at a dose of <0.02 mg/kg. Hence, this was selected as the minimum dose ($D_n$).

In order to determine the number of groups (G) and dose for each group, the relationship between the adjacent dose ratio (r), G, $D_m$ and $D_n$ was determined, as follows: $r^{G-1} = D_m/D_n$. Since r ranges between 1.3 and 1.5, G was calculated as 4. Therefore, the doses for the four groups were 0.020 (D1), 0.029 (D2), 0.042 (D3) and 0.060 mg/kg (D4), respectively.

### *Official test*

Based on the preliminary test, 40 patients were randomly and equally divided into four groups: G1, G2, G3 and G4. The doses of midazolam by intravenous injection were 0.020, 0.029, 0.042 and 0.060 mg/kg, respectively.

All patients fasted for 12 hours and deprived from water for four hours before anesthesia. No premedication was given. In the operating room, an oxygen mask was provided, a vein was cannulated, and Ringer's lactate solution was infused by intravenous drip at 5-6 ml/kg/h. ECG, noninvasive blood pressure, pulse oxygen saturation ($SpO_2$), and the bispectral index (BIS) were routinely monitored. CSEA was administered at L3-4 or L2-3. Approximately 12.5 mg of ropivacaine was given through the subarachnoid space.

In order to identify the anterograde amnesia, pictures were provided ase stimuli after the administration of different doses of midazolam under spinal anesthesia. At 10 minutes after spinal anesthesia (T0), these patients were asked to memorize Picture 1, and a dose of midazolam was intravenously given. Then, these patients were asked to memorize Pictures 2–5 at five minutes (T1), 10 minutes (T2), 15 minutes (T3), and 20 minutes (T4) after midazolam was intravenously giveny. The pictures were presented for five seconds or longer. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), $SpO_2$, BIS, OAA/S score and adverse events were recorded at each time point.

On the morning of postoperative day one, the patients were first asked to independently recall the pictures, and recognize these when shown with the same pictures mixed by two times of the target choice. Accurate memory or recognition was defined as not showing amnesia at that time point. If no amnesia occurred at T1–T4, the patient was considered as not showing amnesia. Then, these patients were inquired of any adverse events. An intraoperative $SpO_2$ <92% was regarded as respiratory depression, and the patient received oxygen through a mask with the jaw raised. Patients with an intraoperative mean blood pressure of <60 mmHg intravenously received 6 mg of ephedrine, and this was repeated five minutes later, when necessary. Intraoperative involuntary movement was restrained using a restraint strap or by dissuasion.

The extent of sedation was evaluated using the Observer's Assessment of Alertness/Sedation (OAA/S) score, as follows: 5, normal response to normal name spoken; 4, lethargic response; 3, no response to normal name spo-

ken, but with response to repeated loudly name spoken; 2, no response to loud naming, but with response to patting or shaking of the head; 1, no response to patting or shaking of the head, but with response to harmful irritation.

### *Calculation of the $ED_{50}$ of midazolam-induced amnesia*

The number of patients that exhibited amnesia was recorded for each group and substituted into the following equations:
$lgED_{50} = SnLgX/Sn$
$SD = d\sqrt{Sp(1-p)/(n-1)}$,
Where, d is the difference between two adjacent doses.

### Test 2

### *Duration of amnesia for an $ED_{95}$ of intravenous midazolam-induced amnesia*

A total of 56 patients were tested, as described for Test 1. The inclusion criteria were also the same as for Test 1. Ten minutes after spinal anesthesia (T0), 0.04 mg/kg of midazolam ($ED_{95}$ for amnesia) was intravenously injected. Different stimulus contents were presented every five minutes, from five minutes (T1) to 70 minutes (T14) after the administration of midazolam, giving 14 memory points. The stimulus included pictures of seven common vegetables and fruits, and animal sounds. Pictures and sounds were alternated. These patients were divided randomly and equally into two teams: Team 1 and Team 2. Team 1 was presented with pictures at T1 and sounds at T2, while Team 2 was presented with sounds at T1 and pictures at T2. The stimulus contents were displayed for five seconds or longer. HR, SBP, DBP, MBP, $SpO_2$, BIS, OAA/S score and adverse events were recorded at each time point.
On the morning of postoperative day one, the patients were asked to independently recall the pictures and sounds, and recognize these from contents mixed by two times of the target. Accurate memory or recognition was defined as not exhibiting amnesia at that time point. Then, long-term memory was tested, and the occurrence of adverse events was recorded.
Based on the follow-up results of the preliminary test, picture and sound amnesia were compared at each time point during the discontinuous test of amnesia.
In order to evaluate memory, since short-term memory lasts only for a few seconds or minutes [2], these patients were presented with a piece of paper with 14 common words (a mix of seven abstract words and seven concrete words) for 30 seconds, and were subsequently asked to recite the words. The number of recited words was recorded as the short-term memory score. Long-term memory lasts for several hours or longer [3]. In order to test for long-term memory, these patients were asked to recall the words the next morning. The number of recalled words was recorded as the long-term memory score. These patients were not shown the words during either of the tests.
Treatments of adverse event during the study and the evaluation of sedative effect were the same as for Test 1.

### Statistical treatment

SPSS software (19.0; IBM SPSS, Armonk, NY) was used for data processing. The values were expressed as mean ± standard deviation (SD). The t-test or U-test was used for intergroup comparisons. Spearman's correlation was used to analyze the relationships between variables and extinction time. Chi-square test was used to compare discrete variables. Probit regression was used to analyze the extinction times $ET_{05}$, $ET_{50}$ and $ET_{95}$ when amnesia disappeared in 5%, 50% and 95% of patients.
A P-value of <0.05 was considered statistically significant.

## Results

### *Test 1: $ED_{50}$ for midazolam-induced amnesia in surgical patients*

There were no significant differences between the four groups at different doses of midazolam in the demographic data (Table I).
None of the patients exhibited amnesia at five minutes after midazolam was given (T1), but all patients exhib-

Table I - *The demographic data of the four groups at the different doses of midazolam.*

| Group (n = 10) | Dose (mg/kg) | Age | Height (m) | Weight (kg) | Male /Female |
|---|---|---|---|---|---|
| G1 | 0.020 | 43.80±9.11 | 1.69±0.07 | 71.90±12.91 | 6/4 |
| G2 | 0.029 | 49.90±5.20 | 1.63±0.08 | 65.10±10.03 | 5/5 |
| G3 | 0.042 | 51.40±5.78 | 1.66±0.08 | 70.00±9.76 | 4/6 |
| G4 | 0.060 | 48.40±9.90 | 1.70±0.15 | 66.30±8.33 | 6/4 |

Table II - *The numbers of patients showing amnesia at the different doses of midazolam*

| Group (n = 10) | Dose of midazolam (mg/kg) | Numbers of patients with amnesia (cases) |
|---|---|---|
| G1 | 0.020 | 0 |
| G2 | 0.029 | 4 |
| G3 | 0.042 | 9 |
| G4 | 0.060 | 10 |

TABLE III - *$ED_{50}$ and $ED_{95}$ for amnesia after administration of midazolam*

| | Results of target dose (mg/kg) | 95%CI (mg/kg) |
|---|---|---|
| $ED_{50}$ | 0.031 | 0.027~0.036 |
| $ED_{95}$ | 0.044 | 0.038~0.071 |

ited amnesia at 10 minutes (T2), 15 minutes (T3), and 20 minutes (T4) after midazolam given. The number of patients who exhibited amnesia in the four groups of different doses of midazolan was from zero to the total number (Table II). .

The model equation used to calculate $ED_{50}$ and $ED_{95}$ was as follows:

PROBIT(P) = 16.773+11.156X

Where, x is the dose of midazolam.

The $ED_{50}$ and $ED_{95}$ values for midazolam-induced amnesia are shown in Table III.

*Test 2: Duration of amnesia at $ED_{95}$ for intravenous midazolam*

In Test 2, 52 of 56 cases were valid, and the valid rate was 92.9%. The age of valid cases was between 18 and 65 years old. There were a total of 45 amnesia cases, which included 23 males and 22 females. The mean weight was 68 ± 9.88 kg.

Rate of amnesia at $ED_{95}$for intravenous midazolam.

None of the patients exhibited amnesia to the words displayed before the administration of midazolam (retrograde amnesia). However, 46 patients (88.5%) developed amnesia to the pictures and sound displayed after the administration of 0.04 mg/kg of midazolam ($ED_{95}$ for amnesia).

*Extinction time at $ED_{95}$ for midazolam-induced amnesia*

The interquartile ranges of the starting extinction time and confirmed extinction time of the administration of 0.04 mg/kg of midazolam ($ED_{95}$ for amnesia) were 15 (18.75) and 30 (25) minutes, respectively.

Using probit regression analysis, dthe extinction times (ET05, ET50, and ET95) for midazolam-induced amnesia were calculated (Table IV). The time of disappearance of amnesia in 5% of patients (ET05) was -6.36 minutes, which was a negative data. Furthermore, ET05 had no significance, and the amnesia rate was 88.5% (rather than 95%) at this time.

All patients received successful anesthesia, and exhibited perfect intraoperative analgesia and normal circulatory values. However, no severe hypotension was noted. Two patients reported nausea within 10 minutes after the administration of anesthesia into the subarachnoid space,

TABLE IV - *The extinction times ($ET_{05}$, $ET_{50}$, and $ET_{95}$) at an ED95 for amnesia of midazolam (n = 52)*

| | Target time (min) | 95%CI (min) |
|---|---|---|
| $ET_{05}$ | -6.36 | no significance |
| $ET_{50}$ | 23.77 | 20.18~27.07 |
| $ET_{95}$ | 53.90 | 48.54~61.47 |

TABLE V - *The adverse events during midazolam sedation (n = 52)*

| Adverse events | (%, patients) |
|---|---|
| Nausea | 3.8% (2) |
| Transient respiratory depression | 23.1% (12) |
| Coughing and nasal itch | 17.3% (9) |
| Excitation and hyperphasia | 19.2% (10) |
| Involuntary movement of limbs | 11.5% (6) |

TABLE VI - *Midazolam-induced amnesia in relation to the OAA/S score (n = 52)*

| | OAA/S score = 5*** | OAA/S score = 4 | OAA/S score ≤3 |
|---|---|---|---|
| Amnesia rate | 9.17 % | 61.75 % | 97.18 % |

but before the injection of midazolam. Nausea was relieved by accelerating fluid replacement, placing the patient in a head-up position, and giving an intravenous injection of ephedrine. The nausea was probably correlated to the excessive dose of anesthesia. Other adverse events occurred within 25 minutes after the intravenous injection of midazolam. These included transient respiratory depression, which was relieved by giving oxygen through a mask with the jaw lifted. The number of adverse events during midazolam sedation is presented in Table VI.

## FACTORS RELATED TO MIDAZOLAM-INDUCED AMNESIA

*BIS*

(1) Fifty percent of the patients were under amnesia, that is, at23.77 min after the administration of midazolam, patients under amnesia had a BIS value of 83 [2]. Five percentof the patients were under amnesia, that is, at 53.902 minutes after the administration of midazolam, the BIS value of patients was 91.

*OAA/S score*

The amnesia rate induced by midazolam increased with

the decrease in OAA/S score, and the amnesia rate significantly differed (P<0.001) between the different sedative levels (OAA/S scores). Midazolam-induced amnesia in relation to the OAA/S scores was based on Table VI.

*Memory tests*

There were no significant differences in memory performance with time after anesthesia for both the picture memory and sound memory tests.

## Discussion

The present results show that $ED_{50}$ and $ED_{95}$ for intravenous midazolam-induced amnesia under CSEA were 0.031 mg/kg (95% CI: 0.027–0.036 mg/kg) and 0.044 mg/kg (95% CI: 0.038–0.071 mg/kg), respectively. Furthermore, the dose and onset time of midazolam-induced amnesia were smaller than those observed with intramuscular or oral administration [4].

With the administration of 0.04 mg/kg of midazolam at $ED_{95}$ for amnesia, the amnesia rate was 88.5%, which was close to the values in other reports [5,6]. The $ET_{95}$ at an $ED_{95}$ of midazolam for amnesia was 53.9 minutes (95% CI: 48.5-61.5 minutes). The $ET_{50}$ was 23.8 minutes (95% CI: 20.2-27.1 minutes). However, the $ET_{05}$ value could not be calculated. The distribution half-life (t1/2a) of intravenously administered midazolam was 0.3 ± 0.24 hours [7], and the optimal effective time was within one hour after administration. The $ET_{50}$ and $ET_{95}$ values for midazolam-induced amnesia in the present study were consistent with its pharmacokinetics [8]. The $ET_{50}$ of midazolam-induced amnesia thad a BIS value of 83, while the $ET_{95}$ of amnesia had a BIS value of 91.

The BIS is a good index of the sedative level and loss of consciousness, and reflects memory [9]. However, it remains controversial whether BIS can predict anterograde amnesia in surgical patientsl. One study reported that after preoperative intramuscular injection of 5 mg of midazolam, a BIS of <90 may indicate the occurrence of amnesia [3]. In another study, after a single intravenous administration of 0.05–0.075 mg/kg of midazolam, a BIS of 80-90 may indicate amnesia of picture memory.10 In the present study, at the same dose (0.04 mg/kg), when the OAA/S score was 5 or 4, BIS was lesser during the amnesia period than in the non-amnesia period.

Consciousness and memory each have a neural anatomical basis, and are considered as two independent concepts [11]. Benzodiazepine-induced amnesia is unique, because it is not related to sedation, at least not causally. Under drug effects, the state of consciousness can also affect amnesia [12], thereby causing sedation–amnesia dissociation.

Generally, the appearance and level of sedation are significantly correlated to amnesia [7]. In the present study, the amnesia rate induced by midazolam increased with the decrease in OAA/S score, and the amnesia rate significantly differed between different sedative levels (OAA/S scores).

It has never been reported whether a difference was present between picture memory and sound memory during midazolam-induced amnesia. Midazolam eliminates only explicit memory, but not implicit memory [13]. Explicit memory implies that the brain should consciously and positively collect experiences, which will be used to complete the present memory, and this involves consciousness in either the storing or reading stage [14]. Although hearing is the last sense to disappear under anesthesia [15], the "last" under consciousness level does not mean "hard to forget". Therefore, the investigators attempted to confirm whether under the consciousness level, midazolam-induced amnesia differed between picture and sound memory. During the confirmed amnesia stage, both picture and sound were forgotten [16]. After the confirmed extinction time, the picture and sound were not forgotten. Thus, all memory times in the suspected amnesia stage were selected to compare the ability to recall picture and sound. No significant differences were found in the amnesia effect between picture memory and sound memory. Thus, it was considered that midazolam has the same effects on the amnesia of pictures and sound.

The investigators determined whether the maintenance time of midazolam-induced amnesia is correlated to a patient's memory ability, and whether, under the same dose of midazolam, amnesia is maintained longer in patients with high memory ability, when compared with low memory ability. In the present study, short-term and long-term memory was both correlated to amnesia maintenance time, especially for short-term memory ability. Memory abilities for both abstract and concrete words were correlated to maintenance time, especially for abstract words. The confirmed extinction time was correlated to the number of words, indicating that the confirmed extinction time is a more objective measure than the starting extinction time in determining amnesia maintenance time.

There were some limitations of the present study. The sample size was small. Thus, the results needs to be further confirmed through larger studies. Furthermore, the investigators proposed some new ideas about midazolam-induced amnesia. However, there were few references on the measures for amnesia maintenance. Hence, the validity and reasonability of these ideas must be further examined.

In the present study, the investigators established the $ED_{50}$ and $ET_{50}$ of midazolam-induced amnesia in surgical patients under CSEA. The correspondence between BIS values and OAA/S scores may provide guidance for the clinical rationale of prophylactic use of midazolam to reduce recall during surgery.

## Forecasts

Although sedative amnesia under local anesthesia can be achieved through many paths for the delivery of midazolam (e.g. oral intake, intravenous injection, intramuscular injection, and continuous pumping), the amnesia maintenance induced by each path or dose should be intensively studied. The optimal method of administration and dose, and the methods to monitor intraoperative amnesia should be further explored.

## Riassunto

Il mantenimento della coscienza intraoperatoria è un incidente grave in anestesia generale. Il Midazolam ha un buon effetto induttore di amnesia anterograda, può prevenire e ridurre l'insorgenza di questo evento negativo. Tuttavia, se il dosaggio di midazolam è controllato in modo improprio, potrebbe non produrre effetti di dimenticanza o portare evidenti effetti collaterali negativi, come depressione respiratoria e ritardo del risveglio. Tuttavia, la mezza dose massima efficace ($ED_{50}$) di midazolam per l'amnesia, la durata dell'amnesia e i fattori che influenzano la durata dell'amnesia sono ancora inconcludenti. Pertanto, è di grande interesse clinico osservare e determinare la dose, la durata e i fattori di induzione dell'amnesia indotti dal midazolam. Ad un totale di 106 pazienti di grado I-II ASA sottoposti a intervento elettivo in anestesia spinale-epidurale sono stati iniettate per via endovenosa diverse dosi di midazolam a 10 minuti dopo l'anestesia spinale-epidurale. Ogni 5 minuti sono state presentate al paziente immagini o suoni con contenuti memorizzabili, e sono stati registrati frequenza cardiaca (HR), pressione sistolica (SBP), pressione diastolica (DBP), pressione sanguigna media (MBP), saturazione di ossigeno nel sangue ($SpO_2$), indice bispettrale (BIS), OAA/S ed eventi negativi. L'amnesia del paziente è stata controllata al mattino presto successivo all'intervento.

RISULTATI: la dose per produzione dell'amnesia nella metà dei soggetti ($ED_{50}$) è stata di 0,031 mg/kg (IC al 95%: 0,027-0,036 mg/kg); la dose per produzione dell'amnesia nel 95% dei soggetti ($ED_{95}$) è stata di 0,044 mg/kg (IC 95%: 0,038-0,071 mg/kg).

Dopo l'iniezione e.v. di 0,04 mg/kg di midazolam, i sistemi respiratorio e circolatorio sono rimasti sostanzialmente stabili, non si sono verificati eventi negativi gravi e la percentuale di amnesia è stata dell'88,5%.

La durata in stato di amnesia per la metà dei soggetti ($ET_{50}$) è stata di 23,77 minuti (IC al 95%: 20,18-27,07 min) e il BIS corrispondente era 83,22.

La durata in stato di amnesia per il 5% dei soggetti ($ET_{05}$) è stato di 53,90 minuti (IC al 95%: 48,54-61,47 min) e il BIS corrispondente era 91,38. L'effetto che induce l'amnesia del midazolam è risultato correlato al grado di sedazione, alla BIS e all'età e non era correlato alla memoria visiva o alla memoria uditiva.

CONCLUSIONE: in questo studio sono stati preliminarmente determinati l'$ED_{50}$, l'$ED_{95}$ e il tempo di mantenimento dell'effetto di amnesia del midazolam per via endovenosa.

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