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The effect of midazolam–thiopental coinduction on recovery in minor surgery

Nur Baykara, Tulay Sahin, and Kamil Toker

Department of Anaesthesiology, University of Kocaeli, Tubitak loj. 4A, Gebze/Kocaeli, Turkey

Abstract
Purpose. The effects of midazolam–thiopental coinduction on recovery were investigated and compared with thiopental induction.
Methods. Fifty patients, ASA 1 or 2, undergoing minor orthopedic surgery, were randomly divided into coinduction and thiopental groups. During preoxygenation, the patients received midazolam 0.1 mg·kg^{-1} (coinduction group) or saline (thiopental group) 1 min before induction of anesthesia with thiopental. Isoflurane and nitrous oxide were used to maintain anesthesia. Isoflurane concentration was adjusted to keep blood pressure within ±20% of the preoperative value. The time to awaken (open eyes, give name and birth-date) and the time to discharge readiness were recorded. Psychomotor tests, including simple light reaction time (SLRT), sedation analogue scale (SAS), and digit span test, were performed pre- and postoperatively.
Results. The induction dose of thiopental was significantly lower in the coinduction group. End-tidal isoflurane concentration during surgery was also lower in the coinduction group. There were no significant differences in awakening times and discharge readiness between the two groups. Although SAS values were lower in the coinduction group than in the thiopental group 8 and 24 h after anesthesia, other test results were similar in both groups. The frequency of nausea and vomiting in the recovery period was lower in the coinduction group.
Conclusion. We conclude that midazolam–thiopental coinduction is a suitable technique when used in conjunction with isoflurane in day-case surgery.

Key words Thiopental · Midazolam · Drug interactions · Recovery assessment · Ambulatory surgery

Address correspondence to: N. Baykara
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Introduction

The combined effect of midazolam and thiopental in anesthetic induction was investigated in previous studies, and it was demonstrated that there was a synergistic interaction between the two agents [1,2]. Both agents exert the majority of their sedative effects via an interaction with the gamma-amino butyric acid A ($GABA_A$) receptor–chloride ionophore [3,4]. Benzodiazepines and barbiturates increase $GABA_A$ complex activity, causing an increase in chloride channel conductance. Barbiturates also enhance the binding of benzodiazepines to the benzodiazepine receptors [4–7].

To date, midazolam–thiopental coinduction has not been studied in relation to the recovery of psychomotor functions. In the present study, we investigated the time to recovery of psychomotor functions with midazolam–thiopental coinduction compared with that for thiopental.

Materials and methods

The study was approved by the Medical Ethics Committee of the hospital. Fifty patients, 18–60 years of age, undergoing minor orthopedic procedures as day-cases were studied. No patients were taking any psychotropic medication, and their body weights ranged from −20% to +20% of ideal weight. Introduction, explanation, and familiarization of the test procedures took place with the patients 24 h before surgery. All the operations were performed between 14.00 and 15.00 hours. Psychomotor tests, including simple light reaction time, sedation analogue scale, and digit span, were applied to all patients and preoperative scores were determined. Patients were randomly assigned to one of two groups: the thiopental group ($n = 25$) or the coinduction group ($n = 25$).

No patient was premedicated. During preoxygenation, patients received 0.1 mg·kg^{-1} midazolam (coinduction group) or saline (thiopental group). One minute later, all patients received thiopental until loss of eyelash reflex. Blood pressures and heart rate were measured before and after induction. Following induction, patients received 0.5 mg·kg^{-1} atracurium for tracheal intubation. Anesthesia was maintained with 33% oxygen in nitrous oxide, and isoflurane concentration was adjusted to keep blood pressure within ±20% of the preoperative value. All patients were monitored by electrocardiogram, automatic blood pressure cuff, finger pulse oximeter probe, and peripheral nerve stimulator. Blood pressure was measured every 3 min. End-tidal CO_2 tension was maintained between 35 and 40 mmHg. At the conclusion of surgery, the anesthetic agents were discontinued and residual neuromuscular blockade was reversed with 20 μg·kg^{-1} atropine and 60 μg·kg^{-1} neostigmine. The duration of anesthesia was recorded. The times to "show tongue" and to answer simple questions (giving name and date of birth) were noted by a physician observer, who was blinded to the anesthetic technique. Thereafter, the patients were transferred to the recovery room. All patients were given 1 g parasetamol and complaints of headache, vomiting, or nausea, etc. were recorded. The time to discharge from the hospital was recorded. Qualification for discharge from hospital was defined by postanesthesia discharge score (PADS) [9].

The digit span test was first carried out after 45 min, and repeated every 15 min until the results become normal. The light reaction time test and the sedation analogue scales (SAS) were evaluated at 1, 1.5, 2, and 3 h after the end of anesthesia. The patients were given a form containing SAS and were asked to complete it at 8 and 24 h after anesthesia at home. All procedures were carried out in a quiet room.

SAS. Sedation analogue scales consisted of five straight lines each of 100 mm in length, and patients were asked to place a perpendicular mark through the scale at the point which reflected the degree of sedation they were feeling at that time (Fig. 1). The average value of points out of the five scales was determined. This value represented the patient's sedation score at that moment. Possible scores in the SAS ranged from 0 (highly alert) to 100 (highly sedated). A score of 50 represented the patient's normal condition.

Simple light reaction time. Using a simple computer program, patients were asked to press a button to extinguish a randomly illuminated light on the computer screen. The simple light reaction time is the period from the appearance of the light on the screen to it being extinguished by the patient. The mean value was determined in milliseconds from 20 recordings.

Drowsy	Alert
Tired	Energetic
Clumsy	Well coordinated
Almost asleep	Wide awake
Fuzzy	Clear headed

Fig. 1. Sedation analogue scales

Table 1. Demographic data of patients (mean ± SD)

	Thiopental group	Coinduction group
Number of patients	25	25
Age (years)	36.2 ± 14.6	32.2 ± 14.6
Weight (kg)	66.8 ± 12.2	72.4 ± 10.2
Sex (M/F)	12/13	11/14
Duration of anesthesia (min)	62.6 ± 7.9	57.0 ± 16.7

Digit span. A series of digits was read to each patient, who was instructed repeating it forward. The same procedure was also carried out repeating the digits backward. The longest series successfully repeated both forward and backward were taken as the baseline values for the individual patient.

All data are reported as the mean ± SD unless otherwise noted. Student's *t*-test was used to analyze the patients' weights and ages, and the Mann–Whitney *U*-test (skewed distribution) was used to evaluate the mean anesthesia time. A comparison of preoperative reaction times was carried out with the Mann–Whitney *U*-test since these values were showing a skew distribution. Student's *t*-test was used for comparing the other reaction times. Comparison of the postoperative 2- and 3-h sedation scores were carried out with the Mann–Whitney *U*-test, since these values were showing a skew distribution. Student's *t*-test was used for comparing the other sedation scores. Significance tests on observed complications were performed by Fisher's exact test.

Results

There was no difference in demographic data between the groups (Table 1). The thiopental doses used in the study were 4.58 ± 0.29 mg·kg^{-1} in the thiopental group and 2.3 ± 0.46 mg·kg^{-1} in the coinduction group ($P < 0.05$). Blood pressure (BP) and HR values were similar between groups before and after induction of anesthe-

sia (Table 2). HR showed an increase after induction, but hypotension (defined as a reduction of mean arterial pressure exceeding 25% of baseline levels) was not observed during anesthesia in either group.

The need for isoflurane was lower in the thiopental group (Table 3). Recovery times from anesthesia and discharge readiness were similar in both groups (Table 4). The frequency of vomiting and nausea during the recovery period was lower in the coinduction group than in the thiopental group (Table 5, $P < 0.05$).

The results of the pre- and postoperative light reaction times were similar for both groups (Table 6). The longest reaction time for both groups was recorded after 1 h of the postoperative period. Then light reaction times for both groups improved over time, but were still impaired after 3 h.

The results of preoperative SAS scores were similar for both groups. SAS scores for both groups showed an initial increase 1 h after of anesthesia, and gradually decreased during the test period, but perceived sedation 8 and 24 h after anesthesia was considerably lower in the coinduction group than in the thiopental group (Table 7).

Even though the normalization of the digit span test was slower in the coinduction group, there was no statistical difference between the groups (Table 4).

Table 2. Systolic (SAP) and diastolic (DAP) arterial pressure (mmHg) and heart rate (HR, beats·min^{-1}) before and after induction (mean ± SD)

	Thiopental group (n = 25)	Coinduction group (n = 25)
SAP		
Before	139.7 ± 18.5	131 ± 17.2
After	125.6 ± 19.6	119 ± 10.4
DAP		
Before	78.1 ± 9.7	77.4 ± 10.3
After	73 ± 9.35	76 ± 16.5
HR		
Before	91.9 ± 29.5	86.8 ± 20.1
After	97 ± 14.2	103.3 ± 16.5

Discussion

In the present study there were no significant differences in awakening times and discharge readiness between the thiopental and coinduction groups. Except for the SAS, which showed the coinduction patients to be less sedated than the thiopental patients 8 and 24 h after anesthesia, the results of the psychomotor tests were similar in both groups. The frequency of nausea and vomiting in the recovery period was lower in the coinduction group.

It is well known that the ideal anesthetic technique for outpatient surgery should provide a rapid and smooth loss of consciousness with an adequate depth of anesthesia and without significant cardiorespiratory changes, followed by a rapid recovery without side effects [9]. Midazolam has less-active metabolites with a relatively shorter plasma elimination half-life than other injectable benzodiazepines, but the use of midazolam as a primary induction agent in day-case surgery is controversial [8–11] because the normalization of psychomotor functions and the amnesic period are considerably longer after anesthesia, even after

Table 3. End-tidal isoflurane concentration during operation (%) (mean ± SD)

	Following intubation				
	10 min	20 min	30 min	40 min	50 min
Thiopental group	1.05 ± 0.19	0.88 ± 0.09	0.89 ± 0.89	0.85 ± 0.22	0.85 ± 0.08
Coinduction group	0.94 ± 0.25	0.65 ± 0.08*	0.60 ± 0.10*	0.62 ± 0.17*	0.66 ± 0.06*

* $P < 0.05$

Table 4. Recovery times from anesthesia and readiness for discharge from hospital (mean ± SD)

	Thiopental group (n = 25)	Coinduction group (n = 25)
Protrude tongue (min)	10.3 ± 3.6	9.6 ± 3.6
Time to give name (min)	16.1 ± 6.3	13.6 ± 3.4
Time to give birth-date (min)	16.9 ± 6.6	14.9 ± 3.6
Short-term learning (min) (digits repeated correctly)	123.6 ± 21.2	131.4 ± 37.6
Discharge readiness (min)	165 ± 18.0	175 ± 19.5

reversal with flumazenil [9]. In order to balance the ratio of desired versus adverse effects, and decrease the costs, the concept of coinduction has attractions for outpatient anesthesia [12]. The effect of coinduction of anesthesia with midazolam and propofol on postoperative recovery is controversial. Elwood et al. [13] showed that the addition of 0.03 or 0.06 mg·kg^{-1} midazolam to propofol induction did not affect the discharge times following minor surgical procedures, even though it delayed eye opening. DeLucia and White [14] compared propofol recovery profiles with the addition of 2 or 5 mg midazolam during induction of anesthesia for ambulatory surgery. Midazolam–propofol coinduction delayed awakening time, but did not delay discharge after anesthesia. Djaiani and Ribes-Pastor [12] reported that the addition of midazolam (0.05 mg·kg^{-1}) to propofol induction delayed the time of discharge from the hospital. In another study, Tighe and Warner [15] investigated the effect of midazolam–propofol coinduction on psychomotor recovery by using psychomotor tests. Coinduction with midazolam reduced psychomotor recovery in the immediate postoperative phase following propofol infusion anesthesia.

In the present study, we investigated the effects of midazolam–thiopental coinduction on psychomotor recovery. Memory is the most central and important cognitive function [16]. In this study the recovery of short-term memory was assessed by the digit span test. There was no distinct difference between the two groups in the results of digit span tests. However, benzodiazepines have varying effects on memory [16]. Tests to assess long-term memory were not used in this study. Studies using long-term memory are also required to assess the effects of coinduction of midazolam–thiopental on memory.

The sedation scores of the two groups showed no significant differences except at 8 and 24 h. Patients in the coinduction group felt themselves to be considerably less sedated at these times than those in the thiopental group. This may be attributed midazolam's short elimination half-life (2–5 h), in addition to the fact that the thiopental dose was considerably lower in the

Table 5. Number of patients with side effects during the recovery period (%)

Side effects	Thiopental group ($n = 25$)	Coinduction group ($n = 25$)
Nausea	8 (32%)	2* (8%)
Vomiting	4 (16%)	0*
Headache	5 (20%)	2 (8%)
Bronchospasm	1 (4%)	0
Respiratory depression	0	0
Dizziness	7 (28%)	5 (20%)

* $P < 0.05$

Table 6. Mean light reaction times in each group throughout the study

	Before operation	Following discontinuation of anesthetic agents			
		1 h	1.5 h	2 h	3 h
Thiopental group					
Mean reaction time (ms)	406.5	716.2	604.2	547.9	529
SD	40.0	103.3	27.8	39.0	36.0
Coinduction group					
Mean reaction time (ms)	396.1	763.7	587.1	560.4	511.1
SD	32.4	128.7	47.7	83.2	85.6

Table 7. Mean sedation analogue scores in each group throughout the study

	Before operation	Following discontinuation of anesthetic agents					
		1 h	1.5 h	2h	3 h	8 h	24 h
Thiopental group							
SAS (mean)	51.2	74.9	70.6	63.9	59.2	57*	52.8*
SD	9.7	8.5	8.1	7.0	5.4	13	9.1
Coinduction group							
SAS(mean)	49.8	78.8	66.6	61.5	56.4	50	42.7
SD	8.5	8.7	6.7	14.5	13.9	11.6	7.2

* $P < 0.05$

coinduction group than in the thiopental group. Furthermore, to maintain the arterial pressure value at ± 20% of the preoperative level in the coinduction group, the isoflurane concentration was kept lower than in the thiopental group, and this may also have contributed to less sedation in the coinduction group. This concurs with a previous finding that a $0.2\,mg \cdot kg^{-1}$ dose of midazolam decreased halothane MAC by 35% [17].

In the coinduction group, the need for isoflurane decreased alongside thiopental. Even though we did not do a cost analysis, we believe that this may be an advantage for outpatient anesthesia clinics. The findings that the incidence of side effects is lower in the coinduction group and that the sedation scores are lower after 8 h are considered additional advantages of midazolam–thiopental coinduction. We have not had the opportunity to compare the results of our studies with others, since there is no study in the literature comparing the effects of midazolam–thiopental coinduction on recovery. We conclude that in day-case patients, midazolam–thiopentone coinduction may be a suitable anesthesia induction technique when used in conjunction with isoflurane.

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