ing treatment, the bispectral index value was maintained between 40 and 50 by adjusting the target concentration of propofol, according to a previous report.[10] Systemic blood pressure was maintained at no less than 80 mm Hg. During treatment, local anesthetic containing 2% lidocaine and 1:80,000 epinephrine was used if considered necessary. After tooth extraction, IV or suppository nonsteroidal anti-inflammatory drugs were used. After treatment, infusion of both remifentanil and propofol was terminated, and the effect of the muscle relaxant was reversed with vagostigmin. The tracheal tube was removed when spontaneous breathing recovered. Patients were permitted to be discharged, according to the standards given earlier.

DATA ANALYSIS

Data were analyzed with JMP 9.0.0 (SAS Institute, Cary, NC). A linear regression was applied to examine the bivariate regression between the primary outcome variable (time to recovery) and all continuous study variables, whereas 1-way analysis of variance was used between the primary outcome variable and nominal study variables. To extract independent variables affecting the primary outcome, possible predictive variables were selected with stepwise regression, for which the cutoff was $P < .25$, followed by a multiple regression (standard least squares).

A logistic regression was used to test the relationship between the secondary outcome variable (agitation) and continuous variables. The Fisher exact test was used between the secondary outcome variable and nominal variables. After selection with a stepwise regression, for which the cutoff was $P < .25$, a multiple logistic regression (nominal logistic fit) was used to extract independent variables affecting the secondary outcome variable.

Results

We enrolled 106 cases in this study. The patients' backgrounds and summaries of anesthetic data are shown in Table 1. GA was started with an IV line in 72.6% of all cases, whereas inhaled anesthetic and oral midazolam were used in 18.9% and 13.2%, respectively. Both inhaled anesthetic and oral midazolam were used in 4.7%. No patient was hospitalized unexpectedly after GA. Time to recovery (mean ± SD) was 95.7 ± 26.6 minutes. Major complications did not occur. Because agitation was observed in 20% of cases, we analyzed factors related to the agitation.

Table 1. PATIENT BACKGROUND AND SUMMARY OF ANESTHETIC DATA

Category	Variables	Data
Patients	Male/female (%)	76.4/23.6
	Age (mean ± SD) (yr)	23.9 ± 9.3
	Height (mean ± SD) (cm)	155.9 ± 16.5
	Weight (mean ± SD) (kg)	53.9 ± 18.7
	Body mass index (mean ± SD)	21.6 ± 4.8
	Autism (%)	62.3
	Cerebral palsy (%)	19.8
	Epilepsy (%)	44.3
	Mental disorder (%)	24.5
Anesthetic	Induction procedure (%)	
	IV line	72.6
	Inhalation (inhalation of sevoflurane)	14.2
	Oral midazolam	8.5
	Oral plus inhalation	4.7
	Duration of infusion (mean ± SD) (min)	110.1 ± 23.4
	Oral midazolam (mean ± SD) (mg/kg)	0.042 ± 0.112
	IV midazolam (mean ± SD) (mg/kg)	0.025 ± 0.022
	Propofol amount (mean ± SD) (mg/kg)	13.9 ± 3.6
	Propofol rate (mean ± SD) ($mg \cdot kg^{-1} \cdot h^{-1}$)	7.70 ± 1.17
	Propofol rate (mean ± SD) ($mg \cdot kg^{-1} \cdot min^{-1}$)	128.6 ± 19.5
	Remifentanil amount (mean ± SD) (mg/kg)	18.2 ± 5.1
	Remifentanil mode (mean ± SD) ($mg \cdot kg^{-1} \cdot min^{-1}$)	0.164 ± 0.044
Surgical/dental treatment	Treatment time (mean ± SD) (min)	88.0 ± 22.3
	Long treatment time (>100 min) (%)	33.0
	Third molar extraction (%)	34.9
Outcomes	Time to recovery (mean ± SD) (min)	95.7 ± 26.6
	Agitation (%)	20.0

NOTE. Continuous variables are given as mean ± SD, and descriptive variables are given as percent.

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Table 2. ALL STUDY VARIABLES VERSUS PRIMARY OUTCOME VARIABLE (TIME TO RECOVERY) (BIVARIATE REGRESSION)

	Pearson Correlation Coefficient	Confidence Interval		*P* Value
		Lower 95%	Upper 95%	
Age*	−0.222	−0.397	−0.032	.018
Gender†	—	—	—	.816
Height*	−0.073	−0.260	0.120	.443
Weight*	−0.120	−0.304	0.073	.207
Body mass index*	−0.103	−0.288	0.089	.276
Cerebral palsy†	—	—	—	.327
Autism†	—	—	—	.973
Epilepsy†	—	—	—	.463
Mental disorder†	—	—	—	.302
Duration of injection*	0.060	0.060	−0.132	.527
Induction procedure† (IV vs oral and/or inhalation)	—	—	—	.103
Induction procedure† (IV plus inhalation vs oral, oral plus inhalation)	—	—	—	.388
Oral midazolam amount*	0.085	−0.108	0.272	.369
IV midazolam amount*	0.072	−0.121	0.261	.445
Propofol amount*	0.179	−0.017	0.355	.060
Propofol rate*	0.142	−0.050	0.326	.134
Remifentanil amount*	0.100	−0.093	0.287	.290
Remifentanil rate*	0.076	−0.118	0.263	.426
Treatment time*	0.097	−0.097	0.283	.309
Long treatment time (>100 min)†	—	—	—	.334
Third molar extraction†	—	—	—	.656

*Linear regression was used for analysis of continuous variables.
†For nominal variables, 1-way analysis of variance was used to compare groups.

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With a bivariate regression, a significant relationship was observed between time to recovery and age (Table 2). Age, mental disorder, induction procedure, IV midazolam, propofol amount, and dental treatment were selected with stepwise regression. In a multiple regression analysis, the amount of IV midazolam and induction with oral midazolam and/or inhalation of sevoflurane were shown to be independent determinants of time to recovery, but not age (Table 3). Because we suspected that age might be a confounding factor, the relationship between age and induction procedure (IV vs oral and/or inhalation) was examined, and there was a significant relationship ($P < .0001$, 1-way analysis of variance).

In a bivariate regression with the secondary outcome of agitation, there were significant relationships with age, height, weight, cerebral palsy, autism, epilepsy, induction procedure, and oral midazolam (Table 4). Age, epilepsy, induction procedure (IV plus inhalation vs oral, oral plus inhalation), and propofol

Table 3. RESULTS OF MULTIVARIATE REGRESSION (STANDARD LEAST SQUARES) WITH PRIMARY OUTCOME VARIABLE (TIME TO RECOVERY) AS INDEPENDENT VARIABLE

Parameter	Estimate	SE	*t* Value	*P* Value (Probability > |*t*|)
Intercept	89.24	13.87	6.44	<.001
Age	−0.37	0.33	−1.13	.260
Mental disorder	−7.41	6.01	−1.23	.221
Induction procedure (IV vs oral and/or inhalation)	−9.04	3.73	−2.42	.017*
IV midazolam amount	370.85	136.52	2.72	.008*
Propofol amount	1.24	0.72	1.73	.086
Third molar extraction	4.56	2.73	1.67	.098

NOTE. $R^2 = 0.156$.
*Significant parameter.

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Table 4. ALL STUDY VARIABLES VERSUS SECONDARY OUTCOME VARIABLES (AGITATION [YES OR NO]) (BIVARIATE REGRESSION)

	Odds Ratio	*P* Value
Age*	0.017	.003
Gender†	1.19	>.999
Height*	0.045	.013
Weight*	0.040	.030
Body mass index*	0.143	.172
Cerebral palsy†	0.00	.012
Autism†	3.95	.037
Epilepsy†	0.272	.040
Mental disorder†	0.521	.394
Duration of injection*	0.177	.235
Induction procedure† (IV vs oral and/or inhalation)	0.152	<.001
Induction procedure† (IV plus inhalation vs oral, oral plus inhalation)	9.81	<.001
Oral midazolam amount*	17.9	.001
IV midazolam amount*	0.334	.181
Propofol amount*	0.359	.545
Propofol rate*	3.56	.407
Remifentanil amount*	1.87	.639
Remifentanil rate*	1.90	.649
Treatment time*	0.445	.411
Long treatment time (>100 min)†	1.08	>.999
Third molar extraction†	0.436	.328

*Logistic regression was used for analysis of continuous variables.

†For nominal variables, a contingency table and Fisher exact test (2 sided) were used to compare groups.

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amount were selected with stepwise regression. In a multiple logistic regression analysis, only age and induction procedure (IV plus inhalation vs oral, oral plus inhalation) were independent predictors of agitation (Table 5).

Discussion

The purpose of this study was to determine factors affecting the outcomes, such as delayed recovery and complications, with a retrospective multiple regression analysis. Results show that the amount of IV midazolam and use of oral midazolam and/or inhalation of sevoflurane are independent predictors of delayed recovery, but not age. Because there was a significant relationship between age and induction procedure (IV vs oral and/or inhalation), age is considered a confounding factor.

In our facility, midazolam was often injected before the injection of propofol. Patients who received midazolam before propofol may have been sedated enough to not respond to the discomfort from the propofol injection. However, because fentanyl has been proven to be effective for pain relief,[11-15] starting a continuous infusion of remifentanil 2 to 3 minutes before the propofol injection is more useful for ambulatory GA than midazolam. Thus, IV midazolam does not seem to have an advantage for ambulatory GA consisting of remifentanil and propofol.

In our study, oral midazolam and/or inhalation of sevoflurane was shown to be an independent predictor of prolonged recovery, although oral midazolam was very useful in patients with a high level of fear. Oral midazolam is reported to not affect recovery time in pediatric patients.[4] Because adult patients are included in this study, prolonged recovery may occur at a higher rate in adults after oral midazolam. In addition, oral midazolam was shown to be an independent factor for agitation.

In our facility oral midazolam was used for patients with a high level of fear, which is considered a reason for agitation when they are awake. Inhalation of sevoflurane during insertion of an IV line may be involved with delayed recovery. However, because the direct effect of sevoflurane used only during induction does not seem to prolong recovery, further research on a larger sample size is necessary to clarify this question.

Although administration of midazolam and/or fentanyl is effective,[16,17] because it leads to delayed recovery, complete prevention of agitation should not be the goal in ambulatory GA. Age is an independent determinant of agitation in our results. This may support previous reports on the importance of coopera-

Table 5. RESULTS OF MULTIPLE LOGISTIC REGRESSION (NOMINAL LOGISTIC REGRESSION) WITH SECONDARY OUTCOME VARIABLES (AGITATION [YES OR NO])

Parameter	Estimate	SE	χ^2	*P* Value (Probability > χ^2)
Intercept	2.34	1.45	2.59	.107
Age	−0.08	0.04	5.19	.023*
Epilepsy	−0.67	0.34	3.78	.052
Induction procedure (IV plus inhalation vs oral, oral plus inhalation)	−0.91	0.35	6.81	.009*
Propofol amount	−0.12	0.08	2.41	.121

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tion from parents.[18] Pain control, by use of local anesthetics and nonsteroidal anti-inflammatory drugs during and after dental treatment, is considered important, especially when GA is maintained with remifentanil because it induces hyperalgesia.[19]

In conclusion, in ambulatory GA with TIVA consisting of remifentanil and propofol, the amount of IV midazolam was an independent determinant of delayed recovery. Oral midazolam contributed to delayed recovery, although it is very useful for induction in patients with a high level of fear. Oral midazolam and a younger age are independent predictors of agitation. In the future, a prospective study with a larger sample size among multiple facilities is expected to validate the suggestions raised in this study.

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