CHAPTER 4

RESULTS

4.1 Demographic data

A randomized double blind cross-over design was used in this study so that each volunteer served as his/her own control. Forty volunteers aged between 23-25 years were recruited into the study. All subjects were healthy, not taking any medications and had no contraindications for the use of N_2O/O_2 inhalation sedation. From total of 40 subjects, 25 were female (62.50%) and 15 were male (37.50%). Mean age of the subjects was 23.21±0.95 years. The mean level of anxiety prior to the N_2O/O_2 administration with the slow titration and rapid induction techniques were 13.05±16.05 and 12.95±13.15, respectively. There was no statistically significant difference in the level of anxiety prior to the administration of both techniques (Paired T-test, p=0.964). Eighty sessions of N_2O/O_2 inhalation sedation were performed in this study (40 sessions of the slow titration technique and 40 sessions of the rapid induction technique). The flow rate ranged from 6-10 L/min, There was no statistically significant difference of the flow rate between techniques (Paired T-test, p= 0.875) Total length of procedures from preoxygenation until after 5 minutes postoxygenation of the slow titration technique ranged from 16-22 minutes (mean 18.17±1.41 minutes) while those of the rapid induction technique ranged from15-21 minutes (mean 17.17±1.13). The statistical analysis showed significant different of the length of procedure between techniques (Paired T- test, p=0.001)

4.2 Clinical Effects

4.2.1 Objective signs

In the slow titration technique, limp legs was observed in 9 subjects (22.50%). Open palms was observed in 7 subjects (17.50%) and eye close was observed in 10 subjects (25%). In the rapid induction technique, limp legs was observed in 10 subjects (25%). Open palm was observed in 13 subjects (32.50%) and eye close was observed in 13 subjects (32.50%). One of the subjects in the rapid induction technique smiled during N_2O/O_2 inhalation sedation but smiling was not observed in the slow titration technique. Comparison of the objective signs between the slow titration and rapid induction techniques was shown in Table 1. There were no significant differences of the objective signs observed between the different groups of administration.

Table 3 Percentage of objective signs observed in N_2O/O_2 administration with the slow titration and rapid induction techniques

Method of administration / Objective signs	Slow titration n/N (%)	Rapid induction n/N (%)	Chi-square p-value
Limp legs	9/40 (22.50%)	10/40 (25%)	0.793 NS
Open palms	7/40 (17.50%)	13/40 (32.50%)	0.121 NS
Smile	0/40 (0%)	1/40 (2.50%)	0.500 NS†
Eye close	10/40 (25%)	13/40 (32.50%)	0.459 NS

NS: not significantly different by Pearson Chi-square analysis. 0.05 level of significance
NS†: not significantly different by Fisher's Exact Test, 0.05 level of significance

4.2.2 Subjective symptoms

Subjective symptoms during N_2O/O_2 inhalation sedation in this study were reported according to the part of the body including head, body, hands, feet, others and overall feelings. Subjective symptoms of both administrative techniques were shown in Table 2. In the head area, three most common reported symptoms in the slow titration technique were no symptom (47.50%), lightheadedness (20%) and heavy (17.50%). In the rapid induction technique, three most common reported symptoms in the head area were the same as the slow titration technique but they were different in order which were no symptom (52.50%), heavy (25%) and lightheadedness (17.50%). Regardless of the administrative techniques, three most common reported symptoms in the body area were light, heavy and tingly. In the slow titration technique, there were 17 subjects (42.50%) reported that their bodies felt light and 12 subjects (30%) reported that their bodies felt heavy whereas 10 subjects (25%) reported that their bodies felt tingly. In the rapid induction technique, light body was reported in 16 subjects (40%), heavy body was reported in 15 subjects (37.50%) and tingly body was reported in 9 subjects (22.50%). Three most common reported symptoms in the hands in both the slow titration and the rapid induction techniques were tingly, heavy and light. Twenty subjects (50%) in the slow titration technique and 22 subjects (55%) in the rapid induction technique reported that their hands were light during N_2O/O_2 inhalation sedation. For heaviness in the hand area, there were 10 subjects (25%) in the slow titration technique and 14 subjects (35%) in the rapid induction technique reported of this symptom. In addition to the upper part of the body, tingly, heavy and light were the three most common symptoms in the feet area in both the slow titration and rapid induction techniques. Fifty-two percent of the

subjects in the slow titration technique and 45% of the subjects in the rapid induction technique reported tingly at their feet during N_2O/O_2 administration. Heavy feet were reported in 25% and 35% of subjects in the slow titration and rapid induction techniques, respectively. The third most common symptom in the feet area was light feet which were reported in 20% and 17.50% of subjects in the slow titration and rapid induction techniques, respectively.

Besides the symptoms of the parts of the body reported above, there were 28 subjects (70%) in both administration techniques reported that they had perioral paresthesia during N_2O/O_2 inhalation sedation. The area of perioral paresthesia included lips, tongue, buccal mucosa and hard palate. Moreover, the subjects in both techniques also reported the alteration of visual and hearing functions. Ten subjects (25%) in the slow titration technique and 13 subjects (32.50%) in the rapid induction technique had the alteration of visual function. The most common symptom reported was blurred visions and inability to focus. In addition to visual alteration, hearing alteration had also been reported in 10 subjects (25%) in each administrative technique and the most common complaint was having a ringing in their ears.

In addition to the subjective symptoms, we also investigated the overall feeling of subjects during N_2O/O_2 inhalation sedation. In the slow titration technique, 24 subjects (60%) reported their feelings to be more comfortable and relax after receiving N_2O/O_2 inhalation sedation. Twelve subjects (30%) felt calm and 4 subjects (10%) felt happy. Eight out of 40 subjects (20%) reported that they wanted to stay still and didn't want to do anything and 5 out of 40 subjects (12.50%) reported that their thinking process was slower than normal and took more time to answer the questions during N_2O/O_2 inhalation sedation. Floating was reported in 13 subjects

(32.50%). During the N_2O/O_2 inhalation sedation with the rapid induction technique, 29 subjects (72.50%) reported that they felt comfortable whereas 11 subjects (27.50%) reported that they felt calm. Four out of 40 subjects (10%) felt happy. Eight (20%) subjects reported that they didn't want to do anything and 5 subjects (12.50%) reported that their thinking process was slower than normal while receiving N_2O/O_2 inhalation sedation. The feeling of floating was also reported in 13 subjects (32.50%) in this technique. When subjective symptoms between the slow titration and rapid induction techniques were compared, no statistically significant differences of subjective symptoms between techniques were found.

Table 4 Percentage of subjective symptoms in each part of the body in the slow titration and rapid induction techniques

Subjective symptoms \ Method of administration		Slow titration % (n/N)	Rapid induction n/N (%)	p-value
Head	Ok	47.50% (19/40)	52.50% (21/40)	0.655 NS
	Lightheadedness	20% (8/40)	17.50% (7/40)	0.755 NS
	Tingly	7.50% (3/40)	2.50% (1/40)	0.615 NS†
	Light	7.50% (3/40)	2.50% (1/40)	0.615 NS†
	Heavy	17.50% (7/40)	25% (10/40)	0.412 NS
Body	Ok	0% (0/40)	0% (0/40)	-
	Tingly	25% (10/40)	22.50% (9/40)	0.793 NS
	Warm	2.50% (1/40)	0% (0/40)	1.000 NS†
	Cold	0% (0/40)	0% (0/40)	-
	Light	42.50% (17/40)	40% (16/40)	0.820 NS
	Heavy	30% (12/40)	37.50% (15/40)	0.478 NS
Hands	Ok	5% (2/40)	0% (0/40)	0.494 NS†
	Tingly	50% (20/40)	55% (22/40)	0.654 NS
	Warm	0% (0/40)	0% (0/40)	-
	Cold	2.50% (1/40)	5% (2/40)	1.000 NS†
	Light	17.50% (7/40)	17.50% (7/40)	1.000 NS
	Heavy	25% (10/40)	35% (14/40)	0.329 NS

NS: not significantly different by Pearson Chi-square analysis, 0.05 level of significance
NS† : not significantly different by Fisher's Exact Test, 0.05 level of significance

Table 4 Percentage of subjective symptoms in each part of the body in the slow titration and rapid induction techniques (continued)

Method of administration / Subjective symptoms		Slow titration n/N (%)	Rapid induction n/N (%)	p-value
Feet	Ok	0% (0/40)	2.50% (1/40)	1.000 NS†
	Tingly	52.50% (21/40)	45% (18/40)	0.502 NS
	Warm	0% (0/40)	0% (0/40)	-
	Cold	2.50% (1/40)	0% (0/40)	1.000 NS†
	Light	20% (8/40)	17.50% (7/40)	0.755 NS
	Heavy	25% (10/40)	35% (14/40)	0.329 NS
Others	Perioral paresthesia	70% (28/40)	70% (28/40)	1.000 NS
	Visual alteration	25% (10/40)	32.50% (13/40)	0.459 NS
	Hearing alteration	25% (10/40)	25% (10/40)	1.000 NS
	Floating	32.50% (13/40)	32.50% (13/40)	1.000 NS
	Stay still	20% (8/40)	20% (8/40)	1.000 NS
Overall	Comfortable and relax	60% (24/40)	72.50% (29/40)	0.237 NS
	Calm	30% (12/40)	27.50% (11/40)	0.805 NS
	Happy	10% (4/40)	10% (4/40)	1.000 NS†

NS: not significantly different by Pearson Chi-square analysis, 0.05 level of significance
NS† : not significantly different by Fisher's Exact Test, 0.05 level of significance

4.3 Physiologic parameters

Three physiologic parameters including blood pressure, heart rate and hemoglobin oxygen saturation were measured in this study. Each physiologic parameter was measured in 5 steps of N_2O/O_2 inhalation sedation which were prior to the procedure as the baseline, preoxygenation, at the ideal stage of sedation, N_2O termination and postoxygenation. The total changes from the baseline of each physiologic parameter at each step were used for statistical analysis.

4.3.1 Blood pressure

We measured blood pressure prior to the procedure to serve as the baseline. Thus, blood pressures which were recorded at the following steps were analyzed in term of the difference from the baseline. The differences of blood pressure (mean±SD) from the baseline at each step of sedation compared within the same administrative technique were shown in Table 3. Table 4 showed the comparison of of the differences of blood pressure at each step of sedation between the slow titration and rapid induction techniques. In all steps of N_2O/O_2 inhalation sedation, blood pressure, both systolic and diastolic were elevated from the baseline in both the slow titration and rapid induction techniques. However, when compared the changes of blood pressure at each step of procedures to the baseline within the same technique using Oneway-ANOVA, there were no statistically significant differences. When compared the changes of blood pressure at each step between the slow titration and the rapid induction techniques using Independent-Samples T test, only the diastolic blood pressure at the postoxygenation showed statistically significant difference between the slow titration and rapid induction techniques ($p=0.034$).

Table 5 The differences of blood pressure from the baseline at each step of sedation in each administrative technique.

Method of administration / Steps	The difference of blood pressure from the baseline in the slow titration		The difference of blood pressure from the baseline in the rapid induction	
	Systolic (mean±SD) (mmHg)	**Diastolic (mean±SD) (mmHg)**	**Systolic (mean±SD) (mmHg)**	**Diastolic (mean±SD) (mmHg)**
Preoxygenation	3.67±8.16	3.30±6.84	5.77±12.19	6.20±9.75
At the ideal stage of sedation	5.30±10.18	5.15±6.92	6.72±12.25	7.40±8.81
N_2O termination	2.67±10.41	2.90±8.05	5.85±12.03	6.50±11.04
Postoxygenation	1.20±9.78	3.17±7.51	5.35±13.05	7.30±9.43
p-value	0.287 NS	0.514 NS	0.967 NS	0.932 NS
NS: not significantly different by One-way ANOVA analysis, 0.05 level of significance				

Table 6 Comparisons of the differences of blood pressure from baseline between the slow titration and rapid induction techniques at each step of sedation

Blood pressure / Steps	The differences of systolic blood pressure from the baseline			The differences of diastolic blood pressure from the baseline		
	Slow titration (mean±SD)	Rapid induction (mean±SD)	p-value	Slow titration (mean±SD)	Rapid induction (mean±SD)	p-value
Preoxygenation	3.67±8.16	5.77±12.19	0.369 NS	3.30±6.84	6.20±9.75	0.138 NS
At the ideal stage of sedation	5.30±10.18	6.72±12.25	0.573 NS	5.15±6.92	7.40±8.81	0.208 NS
N_2O termination	2.67±10.41	5.85±12.03	0.211 NS	2.90±8.05	6.50±11.04	0.100 NS
Postoxygenation	1.20±9.78	5.35±13.05	0.112 NS	3.17±7.51	7.30±9.43	0.034*

NS: not significantly different by Independent Sample T-test analysis, 0.05 level of significance

*: The Independent Sample T-test significance level is 0.05, p-value = 0.034 significantly different

4.3.2 Heart rate

The differences of heart rate (mean±SD) from the baseline at each step of the slow titration and rapid induction techniques were shown in Table 5. The result of this study showed that heart rates at all steps of N_2O/O_2 inhalation sedation decreased when compared to the baseline. Nonetheless, when compared the changes of heart rate at each step to the baseline within the same administrative technique using Oneway ANOVA, we found no statistically significant difference of the changes of heart rate in both the slow titration and rapid induction techniques. Additionally, when compared the changes of heart rate at each step between the slow titration and rapid induction techniques using Independent-Samples T test, we also found no statistically significant difference of the changes of heart rate between techniques at each stage of sedation.

Table 7 The differences of heart rate from the baseline at each step of sedation in the slow titration and rapid induction techniques

Method of administration / **Steps**	**The difference of heart rate from the baseline**		**p-value**
	slow titration (mean±SD)	**rapid induction (mean±SD)**	
Preoxygenation	-3.50±7.26	-5.80±8.73	0.204 NS
At the ideal stage of sedation	-4.00±7.97	-7.30±14.36	0.208 NS
N_2O termination	-6.37±8.65	-8.40±8.39	0.271 NS
Postoxygenation	-5.25±8.12	-7.50±10.39	0.506 NS
p-value	0.126 NS†	0.625 NS†	

NS: not significantly different by Independent Sample T-test analysis, 0.05 level of significance
NS†: not significantly different by One-way ANOVA analysis, 0.05 level of significance

4.3.3 Hemoglobin oxygen saturation

All of the subjects in this study had mean of 99% hemoglobin oxygen saturation at the baseline. There was no hemoglobin oxygen desaturation observed in any subjects in this study. Thus, there were no statistically significant differences in the changes of hemoglobin oxygen saturation from the baseline when compared in each step of procedures in each administrative technique and between different administrative techniques.

4.4 Time to achieve the ideal stage of sedation

To identify that the subject achieved the ideal stage of sedation, the criteria we used were based on objective signs and subjective symptoms together with the questions which indicate that he/she was relax and ready to undergo treatment as if he/she were the patient. Mean time to achieve the ideal stage of sedation in the slow titration and rapid induction techniques were 8.03±1.34 minutes and 6.67±1.30 minutes, respectively. Statistical analysis using Paired T-test indicated the significant difference of the time to achieve the ideal stage of sedation between the slow titration and rapid induction techniques (p=0.00)

4.5 Nitrous oxide concentration

Twenty-three subjects (57.50%) in the slow titration technique and 26 subjects (65%) in the rapid induction technique achieved the ideal stage of sedation with 50% of N_2O concentration. With 40% of N_2O concentration, 13 subjects (32.5%) in the slow titration technique and 12 subjects (30%) in the rapid induction technique achieved the ideal stage of sedation. Four subjects (10%) in the slow titration technique and only 2 subjects (5%) in the rapid induction technique achieved the ideal stage of sedation with 30% of N_2O concentration. Numbers of subjects and concentration to achieve the ideal stage of sedation in both administrative techniques were shown in Table 6. Each percentage of N_2O concentration that subjects required to achieve the ideal stage of sedation in the slow titration and rapid induction techniques were not statistically significant different.

Table 8 Concentration of nitrous oxide to achieve the ideal stage of sedation in each administrative technique

Method of administration / **N_2O Concentration to achieve the ideal stage of sedation**	**Slow titration n/N (%)**	**Rapid induction n/N (%)**	**p-value**
30%	4/40 (10%)	2/40 (5%)	0.675 NS†
40%	13/40 (32.50%)	12/40 (30%)	0.809 NS
50%	23/40 (57.50%)	26/40 (65%)	0.491 NS

NS: not significantly different by Pearson Chi-square analysis, 0.05 level of significance
NS† : not significantly different by Fisher's Exact Test, 0.05 level of significance

4.6 Complications

The complications in both administrative techniques were shown in Table 7. All complications in this study were minor adverse events and dizziness was the most common complication. Four subjects (10%) in the slow titration technique and 9 subjects (22.50%) in the rapid induction technique had dizziness. Nausea occurred in 1 subject (2.50%) in the slow titration technique and 2 subjects (5%) in the rapid induction technique. Four subjects (10%) in the slow titration technique but none in the rapid induction technique reported of uncomfortable feeling. When compared the complications between the slow titration technique to the rapid induction technique, statistical analysis showed significant difference only in the uncomfortable feeling. However, when compared the incidence of overall complications between the slow titration and rapid induction techniques, no statistically significant difference was found. Moreover, none of the subjects in this study had vomiting and major adverse events did not occur.

Table 9 Complications in the slow titration and rapid induction techniques

Method of administration / **Complications**	**Slow titration n/N (%)**	**Rapid induction n/N(%)**	**p-value**
Dizziness	4/40 (10%)	9/40 (22.50%)	0.225 NS†
Uncomfortable	4/40 (10%)	0/40 (0%)	0.116 NS†
Nausea	1/40 (2.50%)	2/40 (5%)	1.000 NS†
Total	9/40 (22.50%)	11/40 (27.50%)	0.606 NS

NS: not significantly different by Pearson Chi-square analysis, 0.05 level of significance
NS† : not significant different by Fisher's Exact Test, 0.05 level of significance

4.7 Level of satisfaction

Before discharge, all subjects were asked to determine the level of satisfaction using VAS. The mean level of satisfaction in the slow titration and rapid induction techniques were 62.17±20.54 and 68.25±24.56, respectively. When compared the level of satisfaction of the slow titration technique to the rapid induction technique using Paired Sample T-test, we found no statistically significant difference of the level of satisfaction between both administrative techniques of N_2O/O_2 inhalation sedation (p=0.149).