CHAPTER 5

DISCUSSION

The principle of N_2O/O_2 administration by slow titration technique is to provide the minimal amount of drug required by the patient to achieve the desired level of sedation. Many advantages of slow titration are previously emphasized in textbooks[4, 6]. However, there are many clinicians that employed rapid induction technique of N_2O/O_2 inhalation sedation in their practices[10]. Moreover, success and safety of N_2O/O_2 administration by rapid induction technique have been reported in several articles[15, 16, 23, 43, 44, 47]. The aim of this study, therefore, was to compare two administrative techniques of N_2O/O_2 inhalation sedation, slow titration and rapid induction techniques, in terms of clinical effects including objective signs, subjective symptoms, and physiologic parameters; time to achieve the ideal stage of sedation; N_2O concentration to achieve the ideal stage of sedation; complications as well as the level of satisfaction.

This study was a double blind cross-over design which one subject received two sessions of N_2O/O_2 inhalation sedation with different administrative techniques. Thus, the subject served as his/her own control. However, the anxiety level prior to the procedure may affect the sedation procedure so we measured the level of anxiety in all subjects prior to all sessions of N_2O/O_2 inhalation sedation. The level of anxiety (mean±SD) in the slow titration and rapid induction techniques were 13.05±16.05 and 12.65±13.15 respectively. Statistically significant difference of the level of anxiety between administrative techniques was not found; thus, we may assume that the status of the subjects in both administrative techniques prior to the procedure were not different.

Clark and Brunick[6] described in their textbook that objective signs which can be observed in a patient who sedated with the appropriate level of N_2O were less active eyes, glazed look appearance or trancelike expression and smiling. In addition to facial expression, relaxation of arms and legs were also reported during N_2O/O_2 inhalation sedation[4]. Houpt et al.[42] employed 50% N_2O/O_2 by rapid induction technique in young children and reported that objective signs observed in their patients were eyes open, tears, trancelike expression, smile, speaking, laughing, hands open, limp legs and feet abduction. And the two most common objective signs observed in their study were open hands (90%) and limp legs (81%). Similarly, the most common objective signs observed in this study were open palms and limp legs. Owing to the property of N_2O which can cause muscle relaxation, open palms and limp legs can be normally observed in a patient receiving N_2O/O_2 inhalation sedation[4]. However, percentages of open palms and limp legs in Houpt et al.[42] study were largely different from ours. The reason of difference maybe that the subjects in their studies were young patients with operative plans; thus, the levels of anxiety might be higher when compared to the subjects in our study who were volunteers without operative plans. Generally, patients who are fearful or uncomfortable may clench on the armrest and his/her leg may be quite stiff when seating in dental chair. After N_2O administration, the relaxation signs may be more obvious in this patient group resulting in higher number of objective signs observed. In addition to the most common objective signs mentioned above, abducted feet, trancelike expression and smiling could also been observed in subjects in the study of Houpt et al.[42]

Nonetheless, only one subject in the rapid induction technique smiled but trancelike expression was not found in our study. Houpt et al.[42] gave the definition of trancelike expression as a subject stare blankly into the space. However, 25% of the subjects in the slow titration technique and 32.50% of subjects in the rapid induction technique of our study reported that they had visual alteration during the N_2O administration which majority of them complained that their eyes couldn't focus and asked for permission to close their eyes. Nevertheless, there were many differences between Houpt et al.[42] study and our study including patients/subjects ages, level of anxiety, plans for operation, and length of procedure. Moreover, observation of the objective signs was subjective; hence, the results of the studies may be different. Additionally, subjects were asked periodically during the procedure to report their subjective symptoms; therefore, the questions might constantly stimulate the subjects to respond so objective signs in sedated subjects were hard to be seen.

Besides the objective signs, subjective symptoms were also investigated in our study. Three most common subjective symptoms in all parts of the body in both administrative techniques were similar in both number and ranking. Dominant symptoms in the area of head were no symptom, lightheadedness, and heavy. In the body, hands and feet, the most common symptoms were tingly, light and heavy. However, our results were different from the study by Houpt et al.[42] which reported that the most frequent symptoms in their study were ok in most parts of the body except fingers where tingly was the most frequent symptom. One possible reason that could explain these differences was the subjects in Houpt et al.[42] study were young children (mean age=7.7 years) thus they might not be able to use the words to reflect their true feelings resulting in the most common subjective symptoms reported in.

most parts of the body in their study were ok. According to Malamed[4], perioral paresthesia or numbness of soft tissues of oral cavity was one of the symptoms at the early to ideal stage of sedation. Houpt et al.[42] also reported that 58% of the subjects in their study had the sensation in their lips; however, they did not describe this in their published study. Likewise, 70% of our subjects in both administrative techniques reported of perioral paresthesia. The areas of perioral paresthesia included lip, tongue, soft palate and buccal mucosa. Although there were numerous studies previously investigated on the use of N_2O/O_2 inhalation sedation in many fields, only few studies had reported the clinical effects of N_2O. The alteration of visual and hearing function during N_2O/O_2 inhalation sedation was rarely reported. However, the visual and hearing alterations were found in our study. Visual alteration presented in 25% and 32.50% in the slow titration and rapid induction techniques, respectively. The most common symptom of visual alteration was inability to focus by eyes. Some subjects asked for permission to close their eyes because of blurred vision. Although trancelike expression was not found in our study, we noticed that it may be one of the signs of visual alteration. Because the ability of eyes to focus reduced, the patient's eyes then became glassy or glazed. Hearing alteration was found in 25% of subjects in both administrative techniques. Most subjects who reported hearing alteration also experienced ringing in their ears. Furthermore, 20% of subjects in both administrative techniques had reported in the delayed thinking process. Wanting to stay still (did not want to do anything) were also reported in 12.5% of subjects in the slow titration and rapid induction techniques. These findings on visual and hearing alteration together with delayed thinking process and wanted to stay still may be the consequence of N_2O which has the property of slight depression on central nervous system (CNS) resulting in alteration of all forms of sensation [4]. However, the limitation of this study was that the subjects were the undergraduate dental students who had basic knowledge of N_2O/O_2 inhalation sedation and some of them had previously experienced N_2O/O_2 inhalation sedation. Thus, biases on the subjective symptoms may occur resulting in high percentages of the subjective symptoms. However, we randomly assigned the subjects to receive administrative technique; therefore, the result of the comparison of subjective symptoms between techniques may not be affected.

Purpose of N_2O/O_2 inhalation sedation in dentistry is to reduce patient's anxiety and fear. Patient's mood may be changed during N_2O/O_2 inhalation sedation; however, it may differ among individual. The overall feelings of subjects in both administrative techniques in this study were shown in Table 2. Most of the subjects in our study reported the overall feelings during N_2O/O_2 inhalation sedation to be comfortable, relax, and calm with similar percentages in the slow titration and rapid induction techniques. This finding confirmed that inhalation sedation with N_2O/O_2 at subanesthetic concentration has anxiolytic effect. Zacny et al.[50] investigated the changes of mood during N_2O/O_2 inhalation sedation in adult patients employing N_2O concentration ranging from 20-50% by slow titration technique. Their study revealed that sensation of happiness and having pleasant thoughts were significantly elevated from prior to N_2O/O_2 administration. Moreover, they also demonstrated that mood changes did not differ between high anxious patients and non-anxious patients.

In term of physiologic parameters, we investigated 3 factors including blood pressure, heart rate and hemoglobin oxygen saturation. Monitoring respiratory rate can be managed in several ways including counting breath or employment of special equipment such as capnograph. Nonetheless, we did not investigate this parameter in our study due to limitation of equipment and unpractical method during the experimental procedure. However, from literature review, N_2O barely affects respiratory system[4, 6]. Decreasing as well as increasing of respiratory rate during N_2O/O_2 sedation has been reported[34, 48]. For heart rates and blood pressures, we analyzed these factors in term of changes from the baseline because we wanted to investigate the true effect of N_2O on cardiovascular system (CVS). Although the subject in our study served as his/her own control, there are some presedation factors that may be variable in such situations, for example, subjects who drink caffeine beverage before N_2O/O_2 inhalation session may have elevated heart rate and blood pressure. Therefore, using the changes of these factors when compared to the baseline at each session would be better representative to investigate the effect of N_2O to CVS.

To evaluate the effect of N_2O to CVS, we monitored blood pressure and heart rate. Blood pressure including systolic and diastolic value and heart rate recorded in each step of procedures of the slow titration and rapid induction techniques were shown in Table 3 and 4. When compared within the same administrative technique, both the slow titration and rapid induction techniques had elevated blood pressures from the baseline at all steps of procedures but statistically significant difference was not found. While comparing the changes of blood pressure between the different administrative techniques, the only statistically significant difference found was the difference of diastolic blood pressure at the postoxygenation step. Another factor to determine the effect of N_2O on CVS was to measure the change of heart rate. The results of this study demonstrated the decreasing of heart rate at all steps of procedure when compared to the heart rate at the baseline in both administrative techniques.

However, statistical analysis either within the same administrative technique or between different administrative techniques failed to show significant difference. Therefore, these findings from this study agreed with the previous reports of the effects of N_2O to CVS that N_2O does not significantly change CVS function and does not produce significant changes in physiologic parameters[4, 6, 48, 75, 76]. Regarding blood pressure, N_2O was reported to have the effect on CVS by mildly depressing myocardial contractibility. Nevertheless, N_2O at therapeutic concentration used in dentistry, has little influence on cardiac output and stroke volume [48]. Therefore, blood pressure of the patient sedated with no more than 50% N_2O usually remains stable. Similarly to the study by Constant et al.[49] who investigated on the effect of 50% N_2O administration by rapid induction technique on the cardiovascular autonomic activity in children and reported that N_2O did not affect mean arterial pressure and did not alter baroreflex; however, N_2O shifted the sympathetic-parasympathetic cardiac balance leading to the predominant of parasympathetic function and resulting in CVS function depression. However, Clark and Brunick [6] stated in their textbook that the effect of N_2O on blood pressure may be dose related and the decreasing of blood pressure during N_2O/O_2 inhalation sedation can be the result of patient's relaxation. Regarding heart rate, similar to blood pressure, N_2O has very little influence on heart rate; thus, heart rate of the patient sedated with N_2O at the subanesthetic concentration usually remains stable [4, 6, 48]. The study of Primosch et al. [34] also demonstrated the significant decrease in pulse rates in children receiving 40% N_2O/O_2 when compared to those who receiving 100% O_2. The results from this study corresponded to their studies. From the overall CVS function, the results of our study demonstrated that, in both administrative techniques, the mean of heart rate was decreased while the mean of blood pressure was increased when compared to the baseline value. These may be the result of physiologic balance of the body systems. During N_2O/O_2 sedation, heart rate can be decreased from anxiety relief, relaxation and comfortable feeling. To maintain the normal function of CVS while heart rate was decreased, blood pressure might be increased for physiologic compensation.

For the last physiological parameters measured in the present study, hemoglobin oxygen saturation, the results of our study showed means of hemoglobin oxygen saturation at all steps were 99% in both the slow titration and rapid induction techniques. In another word, the changes of hemoglobin oxygen saturation from the baseline were not found in this study. This finding was concordant with that of Primosch et al. [34] who reported no changes of hemoglobin oxygen saturation in their study. This may attribute to percentage of O_2 given with N_2O during inhalation sedation. Normally, there are 21% of O_2 in atmospheric air. During N_2O/O_2 inhalation sedation, 30-70% of oxygen is delivered to the patient. The concentration of oxygen that patient breathe during sedation is higher than those in atmospheric air. Therefore, oxygen desaturation is not likely to occur. However, one of the issues that has been the most concern on the use of N_2O/O_2 inhalation sedation is phenomenal of diffusion hypoxia which occurs after N_2O discontinuation. Theory of diffusion hypoxia can be explained that, from the difference of physical properties of nitrogen (N_2) and N_2O which N_2O has partial pressure 31 times greater than N_2, when N_2O is terminated, it diffuses more rapidly from blood stream into lung space than N_2 leaves and, then, dilute oxygen concentration in lung resulting in oxygen desaturation [6]. Generally, decreasing of oxygen saturation lower than 95% after N_2O termination is one of the criteria to diagnosis diffusion hypoxia [24, 31]. Following this issue concerning, giving the patient 100% oxygen 3-5 minutes after procedures has been advocated in textbooks and guidelines [4, 6, 7, 18, 36]. In the present study, we gave all subjects 100% oxygen 5 minutes after N_2O termination in all sessions of N_2O/O_2 inhalation sedation and we did not found any changes of hemoglobin oxygen saturation.

In addition to the differences of physiologic parameters, time to achieve the ideal stage of sedation was one of the factors that we used to compare the differences between the slow titration and rapid induction techniques. Malamed[4] stated in his textbook that the range of 3-6 minutes, not including the preoxygenation stage, was required for the patients to achieve the ideal stage of sedation when slow titration technique was provided. Nonetheless, there were no studies reported the time that patients achieve the ideal stage of sedation with different methods of N_2O/O_2 administration. The average of time to achieve the ideal stage of sedation, including 3 minutes of preoxygenation, in this study were 6.67±1.30 and 8.03±1.34, in the rapid induction and slow titration techniques, respectively. The result of this study showed that the rapid induction technique used significantly less time to achieve the ideal stage of sedation than the slow titration technique did. This finding supported the statement of Clark and Brunick [6] that administration of N_2O/O_2 inhalation sedation by the rapid induction technique was suitable for uncooperative children in order to quickly calm them down. However, they stated in their textbook that they did not recommend this technique for adult patients but the reasons behind this statement was not provided. This recommendation may need to be further evaluated because the advantage of less time consuming with the rapid induction technique may also be beneficial for those highly anxious adult patients.

To identify that the patient achieve the ideal stage of sedation, textbooks recommended observing the patient's signs and symptoms during N_2O/O_2 inhalation sedation. Malamed [4] described in his textbook that, in the early to ideal stage of sedation, symptoms such as lightheadedness, tingly of hands and feet or numbness of soft tissue of oral cavity and signs including slightly elevated of blood pressure and heart rate, decreasing in muscle tone and flushing extremities can be observed in patients. The criteria to identify that subjects achieved the ideal stage of sedation in this study composed of objective signs, subjective symptoms as well as some of the questions that subjects was ready to be treated as if they were patients. Although we had set the criteria to determine that patient had achieved the ideal stage of sedation, we found that it was very subjective and many factors involved. Up until now, there are no specific criteria that can exactly identify the ideal stage of sedation. Therefore, clinicians' experiences in employing N_2O/O_2 inhalation sedation play the most important role in judging that the patient is ready to be treated. Owing to this limitation, time to achieve the ideal stage of sedation may vary between studies and clinicians.

From literature review, no studies have ever demonstrated the N_2O concentration that provided patients the ideal stage of sedation. Only one unpublished data reported 5,000 sessions of N_2O/O_2 inhalation sedation in adult patients, 70% of patients required 30-40% N_2O and only 4% of patients achieved the ideal stage of sedation with 50% N_2O [4]. In contrast to that study, the concentrations of N_2O that the subjects required to achieve the ideal stage of sedation in each administrative technique of this study were shown in Table 6. Regardless of the administrative techniques, majority of the subjects (57.5% in the slow titration technique and 65% in the rapid induction technique) in this study achieved the ideal stage of sedation with 50% N_2O. Some of them required 40% N_2O (32% in the slow titration technique and 30% in the rapid induction technique) and only few of them required 30% N_2O (10% in the slow titration technique and 5% in the rapid induction technique). Surprisingly, the subjects in our study who are dental student volunteers and expected to have low level of anxiety and no operative plan for any treatments required higher N_2O concentration than those patients in that unpublished data reported. Moreover, number of the subjects who achieved the ideal stage of sedation and the N_2O concentrations that provided the ideal stage of sedation did not differ between the slow titration and rapid induction techniques in our study. The difference of two studies may be from that the unpublished data was a retrospective study which certain criteria for the ideal stage of sedation was not provided, the N_2O concentrations reported were retrieved mainly from patients records. Apart from the unpublished data reported, it is also interesting that even in the volunteer subjects, majority of them, required 50% N_2O to achieve the ideal stage of sedation. In real patients especially in emergency situations, the high concentration of N_2O may be required and the successes from employing the products of premixed 50%/50% N2O/O2 in the previous studies were reported [11, 20, 44, 77-79]. However, cautions must be taken when using these products because they are not adjustable. Moreover, they cannot give the patients 100% O_2, thus management of complications occurred during employment of these products may be more difficult. Besides the concentration of N_2O that provide the ideal stage of sedation, James et al.[80] had conducted the study on the effects of N_2O at different attitudes and concluded that the effects of N_2O were decreased at moderate attitudes comparing to sea level. Additionally, Clark and Brunick[6] stated in their textbook that, in Denver, Corolado, with 5,280 feet above the sea level, 5% elevation in N_2O concentration was needed to obtain the same clinical effects as at sea level. Comparing the attitude of where the study took place, unpublished data was conducted at the sea level whereas our study was conducted at 980 feet above the sea level. This was probably one of the etiologies why subjects in our study required higher N_2O concentration than that of previous study [4]. In addition to the difference of altitude, leakage of gas was one of the possibilities that may cause the subjects in this study to require higher N_2O concentration. Klein et al. investigated the end expired N_2O concentration compared to flowmeter settings and revealed that from 30% N_2O delivered from the N_2O delivery system, only 11-12% N_2O reached the patient's respiratory system. It meant that 63% of N_2O concentration had lost from the N_2O delivery system. Furthermore, we used prefabricated nasal hoods as breathing apparatus. Owing to anatomical variations among individuals, they could not create snug fit to all of the subjects noses; thus, some of gas may leak from lack of airtight seal. In addition, nasal hood was normally held in place on the subject nose by its weight; however, the subjects in this study sat in the dental chair in the semi-supine position. Thus, nasal hood's weight did not directly press down on their nose resulting in some degree of gas leakage.

Generally, inhalation sedation with N_2O/O_2 less than the subanesthetic concentration is considered to be an extremely safe procedure [47]. The most common complications from N_2O/O_2 inhalation sedation are minor adverse events which are not life threatening situations. Minor adverse events include nausea and vomiting, dizziness, euphoria, drowsiness, and uncomfortable feeling [4, 6]. From the previous studies, the incidences of minor adverse events were reported to be around 0-6% [13, 23, [41, 46, 54]. Of all the minor adverse events, nausea and vomiting had the highest frequency reported [22, 47]. Major adverse events from N_2O/O_2 inhalation sedation were very rare and they usually happen in compromised patients, using N_2O concurrent with psychiatric drugs or using N_2O more than the subanesthetic concentration [22, 47]. The complications in this study were shown in Table 7. Out of 40 subjects, minor adverse events were reported in 9 subjects (22.50%) and 11 subjects (27.50%) in the slow titration and rapid induction techniques, respectively. The incidence of complications in both administrative techniques was not statistically significant different. The highest frequent complication in both administrative techniques was dizziness. From all of the complications, uncomfortable feeling and dizziness were the major complaints that made the subjects asked for decreasing N_2O concentration in the slow titration technique while dizziness was the major complaint that made the subjects asked for decreasing N_2O concentration in the rapid induction technique. There were no major adverse events in this study. When compared the incidence of minor adverse events of our study to the previous studies [13, 23, 41, 46, 54], our percentages were higher. This may be from the fact that the subjects in our study were volunteers which have none or low anxiety and have no operative plans; thus, they would be likely to be oversedated.

The most common complications found in our study were different from the previous studies. In the previous studies, nausea and vomiting were the most common complications [11, 15, 16, 22, 40]. There were many factors that can cause nausea and vomiting and duration of sedation was one of those factors [4, 22]. Patient who sedated with N_2O for a long duration was predisposed to have nausea and vomiting [4]. However, the duration of sedation in this study was short; the total length of each session of both administrative techniques was no more than 22 minutes; thus, nausea and vomiting may not likely to occur. Besides nausea and vomiting, dizziness was commonly found in patient sedated with N_2O/O_2. Nonetheless, the controversy about dizziness exists. Malamed [4] gave the definition of lightheadedness in the same manner as dizziness and classified lightheadedness (dizziness) as the symptoms at the early to the ideal stage of sedation while another textbook[6] and some articles [11, 23, 41, 54] classified dizziness as the symptom of oversedation or adverse event. In this study, we classified dizziness as the complication of minor adverse event because it was one of the reasons that operator had to decrease N_2O concentration provided to the subjects. The minor adverse events from N_2O/O_2 inhalation sedation were usually transient and the management was simply by decreasing N_2O concentration and observing patient [4]. Complications solved in few minutes after decreasing of N_2O concentration. In addition to minor adverse events, the results of this study supported the previous articles [16, 44, 47] that N_2O/O_2 inhalation sedation alone with no more than 50% N_2O concentration did not cause major adverse events or life threatening situations.

The purpose for the use of N_2O/O_2 inhalation sedation in dentistry is to create the stage of minimal to moderate sedation that reduce patient's anxiety and fear and increase patient's comfort during dental treatment [4]. The slow titration concept has been emphasized for years. It is believed that this technique creates the patient's positive experience and reduces related adverse events [4, 6]. Thus, the level of patient's satisfaction with different administrative techniques is one of the interesting factors to investigate. However, there were limited data reported on this matter. Hennequin et al. [16] investigated 638 sessions on the use of 50% N_2O/O_2 rapid induction technique in young and adult patients and reported the patients' satisfaction to be 91%. In this study, we compared the level of satisfaction between the slow titration and rapid induction techniques using VAS. The result of this study demonstrated that majority of the subjects satisfied with both administrative techniques of N_2O/O_2 inhalation sedation. Surprisingly, the mean of VAS score of the rapid induction technique was higher than those of the slow titration technique although no statistically significant difference was found between them. This finding challenged the contemporary concept of the slow titration technique. However, in this study, we closely monitored the objective signs and subjective symptoms and we chose the adjustable N_2O/O_2 administration machine which allowed us to adjust the N_2O concentration to suit the subject's need. Of all factors that can impact on the level of satisfaction, we thought that monitoring of sedation level and concentration adjustment were the most influential factors on this matter.

Excessive use of N_2O more than necessary may increase office expenditure and can cause negative effects not only to the earth but also to healthcare workers themselves. N_2O leakage has potential to destroy Ozone layer which normally protects the earth from sun rays. Furthermore, for healthcare workers, chronic exposure to N_2O can cause many negative effects to their body systems including reproductive, neurology and hematologic systems [63, 64, 68]. Thus, it is important to employ the appropriate amount of N_2O gas for safety reasons and cost effectiveness. For N_2O/O_2 inhalation sedation, administrative technique may involve the amount of N_2O employment. Besides the administrative technique, other factors including the percentage of N_2O, the flow rate of N_2O/O_2 and length of the procedure may also affect on the total amount of N_2O employment. Although N_2O concentration is gradually increased in the slow titration technique; however, when look at the overall of involved factors, the amount of N_2O employment by the slow titration technique may not differ from the rapid induction technique. However, we did not investigate this subject in our study and further study is recommended.

In conclusion, when compared the slow titration technique to the rapid induction technique of N_2O/O_2 inhalation sedation in the healthy volunteers by using adjustable N_2O/O_2 administration machine, we did not find the statistically significant difference in term of clinical effects, the incidence of complications and the level of satisfaction. Regardless of the administrative techniques, N_2O concentration that majority of the subjects in both administrative techniques in this study achieved the ideal stage of sedation were 50%. The rapid induction technique significantly consumed less time than the slow titration technique did. From the findings of this study, closely monitoring on the clinical effects as well as appropriate concentration adjustment may be more essential factors over the initial administration method.

The limitation of this study was the subjects in this study were all young healthy adult volunteers who did not require any treatments. Satisfaction measurements by VAS score in the volunteers may not be truly reflecting the satisfaction of the real patients. Therefore, the results may differ in different groups of patients and clinical situations. The further investigations to confirm the clinical applications are recommended.