CHAPTER 2

REVIEW OF THE LITERATURE

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2.1 Nitrous oxide and dentistry

Since dental procedures may provoke patient's anxiety and pain especially in children, N_2O/O_2 inhalation sedation providing relatively analgesic, anxiolytic and sedative effects has been used to reduce both pain and anxiety in dentistry. Inhalation sedation with N_2O has been recommended as an alternative to general anesthesia where local anesthesia alone may be inadequate or general anesthesia seems to be overaggressive for dental treatment particularly in patients with medically compromised [7, 25, 26]. With the appropriate patient selection, 83-97% effectiveness of N_2O/O_2 inhalation sedation had been reported in those patients who otherwise required general anesthesia [26]. The crucial characteristics of N_2O that make it popular and preferable in dental treatment which most of the patients are outpatients are its rapid onset and quick recovery. Therefore, the patients can return to their normal activities without residual effects.

Because of its efficacy and ease of use, N_2O/O_2 inhalation for conscious sedation is favored by dentists and apparently widely used in pediatric dentistry. In 1987, the survey on the use of sedative agents in the Canadian pediatric dentists by Wright and Chiasson [27] demonstrated that 50% of the Canadian pediatric dentists used N_2O/O_2 sedation in their patients. From the survey on the use of sedative agents in conscious sedation in the members of the American Board of Pediatric Dentistry by Davis in 1988 [28], 87.6% of dentists in his study used N_2O in their practices. He also reported that the frequency on the use of N_2O was increased markedly from 35% in 1971 to 65% in 1980. The questionnaire survey of the American Academy of Pediatric Dentistry (AAPD) on the relative extent of N_2O use by pediatric dentist by Wilson in 1996 [10] reported that 53% of respondents used N_2O/O_2 more than 5 times per week

and 84.4% of respondents employed N_2O/O_2 at least once a week. Moreover, N_2O/O_2 inhalation sedation in dental setting has long been well accepted by parents of child patients. In the survey of parents' attitude toward behavior management techniques by Lawrence [29] in 1991, N_2O/O_2 sedation was ranked as the second most acceptable technique accordant with the study by Eaton [30] in 2005. Currently, there is no survey on the use of N_2O/O_2 inhalation sedation in Thailand. Regarding the increasing of postgraduate training programs in pediatric dentistry in Thailand, it may be assumed that N_2O/O_2 inhalation sedation is currently widely employed than it was in the past.

2.2 General properties of nitrous oxide

2.2.1 Physical properties of nitrous oxide

N_2O is a non-irritating, sweet smelling, odorless and colorless gas. The molecular weight of N_2O is 44 and boiling point of N_2O is -88.5 °C which exhibits the gas status in room temperature. The specific gravity of N_2O is 1.53 which indicates that it is heavier than air [6].

2.2.2 Pharmacokinetic of nitrous oxide

The blood: gas partition coefficient of N_2O is 0.47 (Table 1). It is relatively insoluble in blood and does not combine with any blood elements or break down in the body. Owing to this property, only small amount of N_2O is required to achieve equilibrium in brain and start its action. Consequently, clinical effects rapidly present within 3-5 minutes. Ninety-nine percent of inhaled N_2O is excreted via lung without

storage or biotransformation in the body [6]. Rate of elimination is equal to the onset of action which is around 3-5 minutes after the N_2O is terminated [4].

At the time N_2O is inhaled into the body, it enters the closed spaces and at the same time replaces the nitrogen (N_2) space. Because of the difference in the partial pressure gradient which N_2O is 35 times greater than N_2, N_2O enters closed spaces more rapidly than N_2 leaves. Therefore, the volumes or pressures of those closed spaces or cavities are increased and the problems may rise in such patients, e.g., bowel obstruction, or tympanoplasty graft. For the same reason, when N_2O is discontinued, absorbed N_2O diffuses out from the blood to the alveolar spaces and dilutes oxygen in lung alveolar resulting in the relatively decreased oxygen saturation in blood stream. This phenomenon is called diffusion hypoxia. The normal level of oxygen saturation is 95% or above. However, if the level of oxygen saturation is between 75-90%, it can be categorized as moderate hypoxemia whereas below 75% is categorized as severe hypoxemia [6]. Therefore, the dropping of oxygen saturation below 95% is identified as oxygen desaturation which is the clinical manifestation of diffusion hypoxia [24]. Additionally, it is believed that oxygen desaturation after the termination of N_2O may cause headache, lethargy and nausea. To prevent these potential adverse events, there is a recommendation to give the patient 100% oxygen for 3-5 minutes after N_2O termination [4, 6]. Since decreased oxygen saturation may occur by the process of N_2O/O_2 sedation, monitoring of hemoglobin oxygenation by pulse oximeter is suggested [5]. Moreover, guidelines for the use of sedation and general anesthesia by ADA have recommended to monitor oxygen saturation by pulse oximeter in addition to the monitoring of circulation system including blood pressure and heart rate pre-, intra- and post-operatively [5]. Despite the significant clinical

concern of this phenomenon, there has been no evidence of the occurrence of diffusion hypoxia following sedation with N_2O at subanesthetic concentration. Quarnstrom et al. [31] evaluated 104 adult patients during and after 35% N_2O/O_2 sedation and reported that none of the patients experienced diffusion hypoxia. Likewise, the study by Dunn-Russell et al. [32] in 1993 compared the giving of 100% oxygen and room air after the patients were sedated with N_2O at concentration lower than 40% in 24 children and revealed no dropping of oxygen saturation below 95%. In another study, Jeske et al. [24] observed 14 adult volunteers who were sedated with 35% N_2O/O_2 and found similar results, no clinical significance of oxygen desaturation.

2.2.3 Mechanism of action of nitrous oxide

The useful characteristics of N_2O in conscious sedation are its analgesic and anxiolytic properties. It is believed that the analgesic property of N_2O is related to the modulation of pain through the endogenous opioid system [6]. N_2O takes its action at a spinal level in brain by activating the release of neurochemical substance of endogenous opioid peptide, e.g., methionine-enkephalin (ME), dynorphin (DYN). Then, these endogenous opioid peptides will activate κ opioid receptors and modulate pain perception via the activation of descending gamma aminobutyric aid (GABA) and noradrenergic pathways [33]. Like the action of opioid drug, the analgesic effect of N_2O can be reversed by naloxone hydrochloride which is the opioid reversal drug [6]. Even though N_2O can decrease pain perception, there are several factors that influence pain reactions such as physical, mental, social or emotional status. Thus,the response to pain stimulation can vary between individuals or even in the same

individual in different situations [6].

The anxiolytic property is the desired effect of N_2O in anxious patients. There are strong evidences that the anxiolytic effect of N_2O associates with the benzodiazepine mechanism in brain. It is believed that N_2O has the capability on the activation of benzodiazepine receptors which subsequently activates gamma-aminobutyric acid type A ($GABA_A$) receptors complex that mediates an anxiolytic signaling pathway [33]. Although it is proved that N_2O modulates anxiety through the benzodiazepine binding site, it remains unknown how N_2O acts at this site in the molecular level.

2.2.4 Potency of nitrous oxide

Potency of vapor anesthetic agent is determined in form of the minimum alveolar concentration (MAC), the percent or concentration of gas that renders 50% of patients unresponsive to a surgical stimulation. N_2O has the lowest potency when compared to other anesthetic agents (Table 1). Moreover, with 104 MAC of N_2O, it indicates that using N_2O alone at atmospheric air is unable to produce the surgical anesthesia [4].

Table 1 Blood: gas partition coefficient and minimum alveolar concentration (MAC) of inhalation anesthetic agents [4].

Agent	Blood:gas partition coefficient	MAC
Isoflurane	1.4	1.2
Sevoflurane	0.65	2.0
Desflurane	0.42	6.0
Nitrous oxide	0.47	104

2.3 Advantages and disadvantages of nitrous oxide use as an inhalation sedation agent

2.3.1 Advantages

First, it has rapid onset of action which is approximately 3-5 minutes. As mentioned above, N_2O has low blood: gas partition coefficient which makes it relatively not soluble in blood thus reaches the equilibrium in brain quickly. Furthermore, when compared with other administrative routes of sedation, e.g., intramuscular and oral routes, the onset of N_2O is more rapid. Second, the depth of sedation is easily adjusted. Thus, the management of oversedated patient is just simply by decreasing the N_2O concentration. Third, it has a flexible duration of action. Since it does not break down in the body, not interact with blood elements and 99% of inhaled N_2O is excreted through the exhalation, the depth of sedation can be altered in few minutes and duration of action is controllable. Fourth, there is no residual effect and it does not compromise patient's activities after N_2O termination. Although minor adverse events may occur during or postoperatively, they disappear in few minutes without any interventions [10, 23, 34]. With all of these advantages, N_2O is appropriate to the outpatient setting.

2.3.2 Disadvantages

Disadvantages of N_2O inhalation sedation are high cost of gas and equipment. Moreover, to achieve the desirable level of sedation, patients should have some degree of cooperation. Therefore, severely anxious or uncooperative child patients may not be suitable for N_2O/O_2 sedation [4]. Moreover, long term chronic exposure to

N_2O is believed to be harmful especially to healthcare workers. More details will be discussed later in topic 4.13

2.4 Indications and contraindications of N_2O/O_2 inhalation sedation

2.4.1 Indications

N_2O has 3 main properties which are analgesic, anxiolytic and amnesic properties that are useful in medical and dental sedations. Nonetheless, the primary purpose of N_2O/O_2 inhalation sedation is to manage patient's anxiety and fear. Thus, mild to moderate anxious patient is the most suitable case for N_2O/O_2 inhalation sedation [35]. Furthermore, patients who gag easily or patients with medically compromised including cardiovascular disease, diabetes, asthma and seizure disorders can also be beneficial from N_2O/O_2 inhalation sedation. Generally, N_2O acts like an inert gas which does not interact with body tissue, it can be used in patient with drug allergy [4].

2.4.2 Contraindications

There are several types of patients who are contraindicated to N_2O/O_2 inhalation sedation. Even though no absolute contraindications are evidenced, appropriate case selection is one of the key to success. According to the Guide to Patient Management for Sedation by Malamed in 2009 [4], patients that are included in the contraindications are patients with a compulsive personality, claustrophobia, children with severe behavior problems, severe personality disorders, upper respiratory tract infection or other acute respiratory conditions, chronic obstructive pulmonary disease (COPD),

patient who does not want to be sedated with N_2O/O_2 and pregnancy. In addition, patients with mouth breathing or abnormal anatomy of respiratory system such as deviated nasal septum, nasal polyps as well as patients who cannot adequately breathe through their noses or patients who cannot tolerate the placement of nasal hood are also not the appropriate cases for N_2O/O_2 inhalation sedation because N_2O will not reach the lung alveolar; hence, it cannot be in the equilibrium. Because N_2O may increase pressure or cause the expansion in closed space, it should be avoided in patients with the condition of pneumothorax, obstructive bowel and middle ear disturbance [6].

2.5 The concentration of nitrous oxide used as a minimal to moderate sedation

According to ADA guidelines, there are three levels of sedation which are minimal, moderate and deep sedations. To manage mild to moderate anxiety and pain control in pediatric dentistry setting, minimal to moderate sedation is usually the goal to achieve. The definition of minimal sedation given by the ADA is the stage of sedation that minimally alters patient's level of consciousness; however, patient is able to respond normally to verbal command and tactile stimulation. Cardiovascular and ventilation functions are preserved. The definition of moderate sedation is the stage that the level of consciousness is depressed by drugs. Patient responds purposefully to verbal command, alone or accompanied by light tactile stimulation. Nevertheless, cardiovascular functions are maintained and spontaneous ventilation is adequate. N_2O/O_2 with appropriate concentration can provide the minimal to moderate stage of sedation. Furthermore, it can be used alone or in combination with

other sedative agents. Although N_2O itself is unable to produce profound surgical anesthesia, it may generate minimal, moderate, deep sedations or general anesthesia when it is combined with other sedative agent(s)[5].

At 5-25% of N_2O concentration, patient's pain threshold is increased. Calm and reduction in spontaneous movement appear. Patient is relaxed and may have the sense of paresthesia area of finger, toes and lip. At 20-55% of N_2O concentration, patient is further relaxed and pain threshold is much more increased. Some abnormal sensations such as abnormal hearing and vision may present. Patients can remain their mouths open with feelings of detachment and expansion of paresthesia[35]. However, if concentration of N_2O exceeds 50%, protective airway reflexes such as laryngeal and pharyngeal reflexes are compromised. Patients become sleepy and do not respond to painful stimuli together with the loss of ability to maintain their months opened. If the concentration of N_2O is increased beyond 70%, patient will lose their consciousness and unable to cooperate which is undesirable for dental treatment [35]. Consequently, there is the recommendation not to exceed 50% of N_2O use for minimal to moderate sedation in dentistry [4].

There is an unpublished study in Southern California which included more than 5,000 sessions of N_2O/O_2 administration and the authors concluded that most of the patients required 30%-40% of N_2O concentration [4]. However, they did not mention the subject selection criteria such as age, type and duration of procedures. Regarding age, since the development of language do not fully establish in young subjects so they cannot exactly explain how they feel. Thus, it is difficult to determine the ideal stage of sedation in young children. Regarding type of treatment and duration of procedure, the patient may need higher concentration of N_2O with the potentially

painful procedures, e.g., extraction and local anesthetic injection, while the concentration of N_2O can be decreased with the simple procedures, e.g., filling and sealant. Moreover, type of treatment also impact on the patient's anxiety and, as mentioned above, the patient's anxiety relates to pain perception. It is commonly found in dental office that young patients have high dental anxiety and fear and they cannot control their feelings so that many of them may present with uncooperative behavior. Because of the sensitivity to pain perception in highly anxious patients, higher concentration of N_2O may be required in these patients when compared to those who have low or no anxiety. In addition, the criteria for the ideal stage of sedation was not clearly described in their study.

2.6 Patient assessment

Because N_2O/O_2 inhalation sedation is not suitable and safe for all patients, it is necessary to assess the patient's physiological and psychological status so that the appropriate patient management can be selected. According to the ADA, patients with the American Society of Anesthesiologists (ASA) class I (healthy patient) and ASA class II (patient who has mild to moderate system disease that are well controlled) are candidates for N_2O/O_2 inhalation sedation in dental setting [5]. Contraindications described previously also exclude patients from using N_2O/O_2 inhalation sedation.

Preoperatively, medical history of the patient should be reviewed and the baseline vital signs must be recorded. The recommended monitoring of vital signs for minimal sedation are blood pressure, pulse rate and respiratory rate but oxygen

saturation should also be included into vital sign information [6]. In children, parents or guardians should be advised of the intent of the procedure, risks and benefits of its use. Informed consent must be obtained at each visit of N_2O/O_2 administration.

It is still controversial whether to fast or not prior to N_2O/O_2 inhalation sedation. Clark and Brunick stated in their book that fasting prior to N_2O/O_2 inhalation sedation is not necessary [6]. Malamed also agree with this and suggests that, fasting for a long time, especially in children, may lead to uncomfortable feeling, uncooperative behavior, and even nausea and vomiting itself [4]. Although fasting may not be a prerequisite for N_2O/O_2 inhalation sedation, light meal such as toast and clear liquids at least 2 hours before an appointment has been recommended [4, 36]. However, Kupietzky et al. [37] demonstrated that there was no significant difference of the frequency of vomiting between fast and non-fast children who were sedated with 50% N_2O by rapid induction technique.

During N_2O/O_2 sedation, vital signs must be monitored continuously and the patient's level of consciousness should be observed [4, 6]. Monitoring in this period must include oxygenation, ventilation and circulation [5]. Monitoring of oxygenation is to ensure that the patient has adequate oxygen saturation. Oxygen saturation can be accomplished by using pulse oximetry which is helpful in early detection of oxygen desaturation. In addition to pulse oximetry, color of mucosa or skin should be observed throughout the procedure. Monitoring of ventilation helps clinicians to early detect and reduce the risk associated with moderate sedation. Besides respiratory rate, ventilation monitoring can be accomplished by observation of the patient's chest movement or excursion of reservoir bag. Monitoring of circulation composes of blood pressure and heart rate that should be recorded pre-, intra- and post-operatively.

Because patient is at risk to deepening sedation, the patient's level of consciousness should be evaluated periodically [4].

2.7 The administrative techniques of N_2O/O_2 inhalation sedation

Currently, there are two administrative techniques in the literature review: slow titration and rapid induction techniques. Both techniques also have advantages and disadvantages. There have been controversies on the administrative techniques of N_2O/O_2 inhalation sedation. Below are the discussions of both administrative techniques.

2.7.1 Slow titration technique

Slow titration technique is the technique that starts giving the patient with low concentration of N_2O usually at 10-20%. Then, 5-10% N_2O is gradually added to the patient at every 30-60 seconds [4, 6, 35]. The operator observes the patient's clinical signs and symptoms and adjusts N_2O concentration until the patient reaches the ideal sedation stage. Slow titration has long been recommended by many authors as the standard technique of N_2O/O_2 administration [4, 6, 8, 35].

The principle of slow titration technique is the belief of biovariability between individuals. Patients respond varyingly to the amount of drug and the dose used in the previous visit does not reflect the amount of N_2O that the patient will need in the next visit. Moreover, with different procedures, patient will require different dosages of N_2O. For example, some phases of treatment such as local anesthetic injection or extraction are potentially painful; operators may consider increasing the concentration

of N_2O in these situations whereas simple procedures such as filling or sealant, the concentration of N_2O can be decreased [6].

From the unpublished data of the University Of Southern California School Of Dentistry, the concentrations of N_2O/O_2 inhalation sedation of more than 5,000 sessions were recorded, most of the patients in that study required approximately 30-40% of N_2O and took 3-6 minutes to achieve the stage of ideal sedation. However, approximately 12% of the patients required the percentage of N_2O lower than 30% and 18% of the patients required the percentage of N_2O higher than 40% [4].

There are many advantages of the slow titration technique. First, this technique is claimed to be safe for both patients and medical personnel [4]. Since only the amount of N_2O required by the patient is employed, minimal leakage or excessive gas will expose to these personnel [38]. Second, slow titration technique will encourage the positive experience for the patient by minimizing the occurrence of oversedation that may cause uncomfortable feeling of the patients during sedation [4]. Moreover, slow titration technique also decreases the rate of the occurrence of adverse events such as nausea, vomiting and euphoria [4]. Third, it was mentioned above that there is biovariability between individuals, thus, giving N_2O by the slow titration technique is recognized as the way to appropriately treat each individual patient [6]. Fourth, not only N_2O, drug administration by titration technique will help the operator to early detect the unpredictable reactions [6].

Even though the slow titration technique has been recommended not only in the textbooks [4, 6] but also in the several guidelines by many organizations [7, 36, 39], there are many dentists that do not use this technique in their routine practices. The survey of the AAPD members showed that only 59.5% of participants employed N_2O/O_2

administration by the titration technique [10]. Moreover, there are many investigators that did not use the slow titration technique in their studies [11, 15, 22, 37, 40-44]. This information reflects the reality of N_2O/O_2 administration technique used in the dental communities.

2.7.2 Rapid induction technique

In contrast to the slow titration technique, the rapid induction technique is defined as the technique starting with high concentration of N_2O and the percentage of N_2O is minimally adjusted to suit the patient's need [6]. In rapid induction technique, the concentration of N_2O that usually employed is 50% and minimal adjustment is approximately ± 10% of N_2O concentration.

For years, N_2O/O_2 inhalation sedation by rapid induction technique has long been practiced by clinicians. Despite many advantages of the slow titration technique mentioned above, many researchers employed N_2O/O_2 administration by the rapid induction technique in their studies both in medical and dental fields [11, 15, 16, 21, 44]. Although the rationale on the N_2O administration by rapid induction technique does not clearly exist, this technique may provide great benefit in some situations such as quickly calm the patient who has intense fearful or uncooperative child. However, Clark and Brunick do not recommend using rapid induction technique in adult patients [6].

Moreover, there are products of a ready to use premixed 50% N_2O and O_2 in a single cylinder on the markets, e.g., Kalinox™ and Entonox™. These products were first introduced in medical practice in 1965 [14]. Subsequently, they were introduced into dentistry and there were few publications that investigated the premixed N_2O/O_2

in dental field. Quarnstorm and Mar [21] demonstrated that 24 of 32 subjects in their study received the adequate sedation and had good tolerance with the premixed of 50% N_2O/O_2 inhalation sedation. Hennequin et al.[16] studied on the efficacy and safety of premixed N_2O/O_2 (Kalinox^{TM}) of 549 patients with 638 sessions of dental treatment. Their study yielded 93.7% of success in sedation and treatment. No incidence of major adverse events and 10% of minor adverse events such as euphoria, nausea and vomiting had been reported in their study. Because there is only single cylinder, the advantages of its usage are fewer appliances required, easy to carry and use. With the fixed concentration of N_2O in the container, there is no chance to accidentally give the patient 100% of N_2O [21]. However, the disadvantages of premixed 50% N_2O/O_2 are its inability to give 100% oxygen to the patient in postoperative treatment which raises the issue concerning diffusion hypoxia and the unadjustable N_2O concentration leading to oversedation of some patients.

Regarding the concern of safety and adverse events of premixed 50% N_2O/O_2, many investigators had studied on this matter. The retrospective study of adverse events of premixed 50% N_2O in children by Gall et al. [23] showed that occurrence rate of minor and major adverse events were 5% (357 of 7,511) and 0.33% (25 of 7,511), respectively. Annequin et al. [44] surveyed on the use of inhalation sedation with fixed 50% N_2O/O_2 in 1,019 administrations and showed that most of adverse events were minor and the majority of minor adverse events were euphoria (20%), dream (5.7%) and nausea and vomiting (3.7%) whereas none of serious adverse event was noted in their study. Similar to the study by Onody et al. [22] in 35,828 administrations of 50% N_2O in children and adult patients, they reported 4.4% of the overall adverse events and 0.03% of these were serious adverse events that were possibly attributed to the

N_2O/O_2 premixed. They also concluded that the premixed 50% N_2O/O_2 was safe for painful procedures in both children and adults. Additionally, Faddy and Garlick [45] had conducted a systematic review on the safety and the efficacy of 50% N_2O on pain relief in prehospital setting by the first responders who are not trained as an emergency technician. In summary of their review, they supported that 50% N_2O was a safe and effective analgesia with minimal side effect without serious adverse events, e.g., hypotension or oxygen desaturation. Moreover, they also suggested that 50% N_2O may be safe even if it was employed by the person who is not in the medical field but has appropriate training.

One of the main disadvantages of premixed 50% N_2O/O_2 in single cylinder is its inability to administer 100% oxygen to the patient postoperatively, leading to the traditional belief of diffusion hypoxia. However, there were several studies investigated on the premixed 50% N_2O/O_2 and failed to demonstrate the occurrence of diffusion hypoxia or oxygen desaturation following 50% N_2O/O_2 administration [11, 13, 15, 16, 21-24, 46].

With the relatively high concentration of N_2O use in the rapid induction technique, the chance of N_2O leakage is higher than in the lower concentration used in the slow titration technique. Hence, the operators and assistants may be at risk from chronic exposure to N_2O. Moreover, N_2O that leaks into the ambient air has potential to destroy the ozone layer which protects the earth from harmful sun rays. Not only has the pollution concern, the employment of high concentration of N_2O also increased the office's expenditure.

Despite the slow titration technique has been advocated to create patient's positive experience with N_2O/O_2 inhalation sedation, the rapid induction techniques

was also well accepted by patients. Ninety-one to one hundred percent of the patients' satisfaction with 50% N_2O/O_2 inhalation sedation by rapid induction technique had been reported [16, 42].

From literature review, both slow titration and rapid induction techniques of N_2O/O_2 inhalation sedation have their advantages and disadvantages. Some studies employed slow titration technique whereas some studies employed the rapid induction technique. Thus, there are controversies regarding both administrative techniques of N_2O/O_2 inhalation sedation.

Up to date, there have been no studies comparing the clinical effects of N_2O/O_2 inhalation sedation of two different administrative techniques; the slow titration and rapid induction techniques. Moreover, only few studies had reported the physiologic parameters and the patient's satisfaction with N_2O/O_2 inhalation sedation and, also, no comparison between these two administrative techniques.

Even though N_2O itself has rapid onset of action which, with slow titration technique, the patient can achieve the ideal stage of sedation within 3-5 minutes [4, 6], the rapid induction technique may also useful to calm the patient with intense fearful in a shorter period. However, time to achieve the stage of ideal sedation by rapid induction technique has never been reported. Additionally, there is a diversity of the concentration of N_2O used in N_2O/O_2 inhalation sedation. There was an unpublished data demonstrated that most of the patients require 30%-40% of N_2O concentration in N_2O/O_2 inhalation sedation whereas 50% of N_2O by rapid induction technique was reported by numerous of studies for the safety and effectiveness of its use[16, 22, 45, 47]. Moreover, none of studies have ever conducted in Thai population.

2.8 Clinical effects

Clinical effects compose of objective signs, subjective symptoms and physiologic parameters. Objective sign is defined as the sign that can be observed from the patient and subjective symptom is what the patient reports during N_2O/O_2 administration. Objective signs and subjective symptoms observed in the patient who is sedated with N_2O/O_2 inhalation sedation may be different in each individual even with the same N_2O/O_2 concentration. However, some of objective signs and subjective symptoms can be used to identify the ideal stage of sedation and the oversedation of N_2O/O_2 inhalation sedation. On the contrary to objective signs and subjective symptoms, physiologic parameters are measured by using devices such as blood pressure meter and pulse oximetry. There are many parameters of physiologic parameters including respiratory rate, heart rate, blood pressure, and hemoglobin oxygen saturation. According to ADA recommendation[5], the monitoring for N_2O/O_2 inhalation sedation is focus on blood pressure, heart rate, and hemoglobin oxygen saturation.

2.8.1 Objective signs and subjective symptoms of ideal sedation

After 3-5 minutes of administration of N_2O at the subanesthetic concentration, clinical signs and symptoms will appear. Clinical signs and symptoms may be different between patients. The common clinical signs and symptoms of N_2O/O_2 inhalation sedation are presented in Table 2.

The ideal sedation stage is the stage that patient is relaxed and comfortable. This stage is the most suitable period to start dental treatment. Symptoms and signs at the ideal stage of sedation are presented in table 2. During the low concentration of

N_2O/O_2 administration, patient will feel happy and has twinkling eyes. Tingling of fingers, toes, cheeks, lips, tongue, head, or chest may be felt. Furthermore, patient will show signs of relaxation such as legs and arms are in relaxed manner. The clinical sensations which may indicate that patient is at the desired level are heaviness, warmth, and floating. However, patient remains aware to surrounding and coherent to the operator's direction [6]. In the study on clinical effects of 50% N_2O/O_2 in children, Houpt et al. [42] reported the several signs including tracelike expression, smile, speaking, laughing, hands open, limp legs and feet abduction appeared during N_2O/O_2 administration. Of all these signs, open hands and limp legs were the most common signs observed. In addition to objective signs, subjective symptoms reported in their study included heaviness, lightness or tingly sensation in the area of head, abdomen, fingers and toes. The feelings of sleepiness and warmth of fingers and abdomen were the group that had significantly higher frequency in their report.

Table 2 Symptoms and signs of ideal stage of N_2O/O_2 inhalation sedation.[4]

Symptoms	Signs
- Lightheadedness - Tingling of hands and feet - Wave of warmth - Feeling of vibration throughout body - Numbness of hands and feet - Numbness of soft tissues of oral cavity - Feeling of euphoria - Feeling of lightness or heaviness of extremities - Analgesia	- Blood pressure, heart rate elevated slightly early in procedure then return to baseline values - Respirations are normal, smooth - Peripheral vasodilation - Flushing of extremities, face - Decreased muscle tone as anxiety - decreases (arms and legs relax)

2.8.2 Objective signs and subjective symptoms of oversedation

When a high concentration of N_2O is used, patient's level of sedation may be altered to a deeper sedation level intended. Patients may become uncooperative or feel uncomfortable with their bodies such as feeling too heavy, too hot or too warm. The patients may lose their normal response to verbal command or take a longer time than usual to respond. Some patients may complain of nausea and vomiting. Dreaming or speaking incoherently is also considered to be signs of oversedation. Patients may talk about their fantastic dreams or have uncontrolled laughing. The detachment or dissociation from environment is possible. Moreover, uncoordinated movement caused by lightweight or floating sensation may present in oversedated

patient. Patients may lose the ability to maintain their mouths opened or may have spontaneous mouth breathing [4, 6]. The management of oversedation is to decrease 5-10% N_2O concentration immediately after the operator has detected that the patient has become oversedated and the patients should be closely monitored of signs and symptoms until they return to the desired level of sedation. Not only does the high concentration of N_2O deepen the sedation level, but also the duration of its use. Therefore, in long duration use of N_2O/O_2, patient's level of sedation may become deeper without the increase of N_2O concentration [4].

2.8.3 Effects of N_2O/O_2 inhalation sedation to physiologic parameters

To provide the proper monitoring for the patient during N_2O/O_2 inhalation sedation, operator should know how N_2O interacts to the body systems. This review will focus on two body systems which are cardiovascular and respiratory systems because they are crucial for vital life.

The effects of N_2O on the cardiovascular system can be determined in terms of blood pressure and heart rate. N_2O slightly depresses myocardial contraction [4] but does not cause significant negative effect on cardiovascular system [6]. Thus, the patient's blood pressure and heart rate during N_2O/O_2 inhalation sedation may not change significantly when compared to the baseline [4, 48]. However, blood pressure may decrease during N_2O/O_2 administration because of the reduction of the patient's anxiety and fear [6]. In addition to patient's anxiety relief, concentration of N_2O used may also relate to the change of blood pressure [6]. However, at subanesthetic concentration, N_2O has a very few effects on cardiac output, stroke volume and heart rate [48]. The study in children (5-9 years old) by Primosch et al. [34] showed the

decreasing in pulse rate of children who received 40% N_2O when compared to those who received 100% oxygen. While Constant et al. [49] demonstrated that the administration of 50% N_2O in children slightly depressed cardiovascular function but did not affect mean arterial pressure.

Besides the cardiovascular system, the respiratory system should also be discussed. Respiratory system can be determined in terms of respiratory rate and hemoglobin oxygen saturation. If N_2O is used as a single agent for mild to moderate sedation, it usually does not depress ventilation. Thus, in healthy patients, respiratory rate remains stable [48]. However, the changes in respiratory rate may occur but not from the effect of N_2O itself. Lower respiratory rate is more likely to result from the reduction of patient's anxiety during sedation [4]. Although respiratory rate may slightly decrease, hemoglobin oxygen saturation is unaffected. Primosch et al.[34] had demonstrated that respiratory rate was significantly decreased but significant change in hemoglobin oxygen saturation was not found in children who sedated with 40% N_2O.

Currently, there are few studies that reported physiologic parameters during N_2O/O_2 inhalation sedation. However, there is no investigation comparing the effect of N_2O on physiologic parameters between two different administrative techniques, the slow titration and rapid induction techniques.

2.9 Recovery from N_2O/O_2 inhalation sedation

Because sedation with N_2O in dental setting is usually done in outpatient department, assessment of patients before allowing them to leave the dental office is

crucial. During the N_2O/O_2 administration, the patient's normal perception may be altered, e.g., drowsiness, floating, lightheadedness or drunk. Therefore, the patients' feelings should return to normal before they are discharged [6]. The mood changes during N_2O/O_2 inhalation sedation had been studied in 45 subjects and the results showed that at the recovery most of the patients' mood changes returned to the baselines [50].

Although N_2O itself has a few effects on cardiovascular systems [49], vital signs which indicate the state of cardiorespiratory systems, including blood pressure, heart rate and rhythm, and respiratory rate should be recorded both pre- and post-operatively [4]. The fluctuation in either positive or negative directions of these values may be seen in the recovery period but it should be in the acceptable range. Malamed [4] has recommended the normal variations of vital signs as follows; blood pressure: ± 20 mmHg/10 mmHg from baseline; heart rate: ±15 beats/min from baseline; respirations: ±3 breaths/min from baseline. While another recommendation from Clark and Brunick [6] stated that when compared to the baseline values measured preoperatively, ±10 mmHg of blood pressure for both systolic and diastolic, pulse rate with 10 beats and respiration rate within 5 beats are acceptable for normal fluctuation.

The impairment of psychomotor function also occurs in N_2O/O_2 inhalation sedation. The assessment of psychomotor performance in 12 adults by using 6 neuropsychological tests to evaluate recovery after prolonged (90 minutes) of nitrous oxide sedation by Conry et al. [51] demonstrated that N_2O had the effects on psychomotor function by compromising fine manual dexterity and impairment of verbal fluency but vigilance, immediate memory and mental tracking ability were preserved. While the study on psychomotor responses to N_2O/O_2 sedation during

dental treatment in 82 subjects by Ayer and Getter [52] demonstrated that N_2O impaired psychomotor function minimally. In their study, they used Reusch color test and peg board test which were used to evaluate the visual motor functioning and visual motor coordination, respectively. Moreover, they also stated that this impairment was rapidly and completely reversible almost immediately after N_2O was terminated. Although there are many tests used to determine the psychomotor performance, it is believed that the most valuable test to assess the recovery of the psychomotor impairment from inhalation sedation is the Bender Motor Gestalt Test [4]. The Bender Motor Gestalt test or the Trieger test, which was developed by Norman Trieger in 1974, aims to measure the sensory-motor performance by connecting the series of dots. With the reliability and validity of this test, it is evident and helpful to determine if the patient has returned to pre-anesthetic baseline level at the recovery period[53].

After N_2O is terminated, the recovery time usually takes around 2-4 minutes. However, Malamed [4] has recommended to give the patient 100% oxygen postoperatively for 5 minutes before taking the nasal hood off. He believes that 100% oxygen will protect the patient from diffusion hypoxia and patient will recover from N_2O/O_2 sedation during this procedure. Additionally, he also advises to leave nasal hood on the patient until he/she feels normal and this may take longer than 5 minutes because the patient who receive long period of N_2O may require longer duration in recovery.

2.10 Complications of N_2O/O_2 inhalation sedation

Complications of N_2O inhalation sedation are categorized into minor and major adverse events. Major adverse events are the followings; respiratory complications such as oxygen desaturation below 95%, airway obstruction, pulmonary aspiration or apnea; cardiovascular complications such as bradycardia, cardiovascular instability; oversedation, e.g., loss of verbal contact more than 5 minutes during procedure. Minor adverse events include euphoria, nausea, vomiting, dizziness, light headedness and paresthesia. The most common adverse events of sedation with N_2O in the subanesthetic concentration (lower than 50% nitrous oxide) are minor adverse events, mostly nausea and vomiting [11, 16, 40, 50]. A number of studies have reported incidence of nausea and vomiting to be around 0-6% [23, 41, 46, 54]. Moreover, the use of N_2O is classified as one of risk factors of postoperative nausea and vomiting both in children and adults[55]. The factors associated to the occurrence of nausea and vomiting are presence of food in stomach, frequent adjustment of N_2O concentration-called 'roller coaster ride', long duration of nitrous oxide administration, past history of nausea and vomiting and high concentration of N_2O [4, 36]. Consequently, Malamed [4] recommends to fast prior to N_2O/O_2 sedation. The fasting guidelines are 4-6 hours for heavy meal and 2 hours for light meal and liquid to prevent or minimize nausea and vomiting [4]. However, Babl et al. [54] reported 71.1% of patients sedated with 50-70% N_2O in their study did not meet the fasting criteria and none of them suffered from serious adverse events and the most common adverse event in their study was nausea. They also revealed that whether patient met or did not meet the fasting guideline, there was no difference in the rate of emesis. Likewise, Kupietzky et al. [37] demonstrated that the parameters including N_2O flow, treatment time and type of treatment in children who

fasted 6 or 1 hours prior to the dental treatment did not result in significant difference of the occurrence of vomiting and vomiting occurred in only 1(1%) subject in their study. In addition to the fasting status, hypoxia and oversedation may also be the causes of nausea and vomiting [4].

Major adverse events are very rare and there were few studies reporting of its occurrence. Gall et al. [23] studied the use of 50% premixed N_2O/O_2 in 7,511 procedures in young patients and reported the incidences of minor and major adverse events to be 5% and 0.3% respectively. However, all cases of major adverse events were self-resolved in minutes without airway intervention. They also indicated that age and addition of psychotropic drugs were the main factors associated with the major adverse events. Babl et al. [46] compared the depth of sedation and complication of 50% - 70% N_2O/O_2 in 762 pediatric patients and demonstrated that patients who were sedated with 70% N_2O/O_2 had level of sedation deeper than those who were sedated with 50% N_2O/O_2. They also reported that vomiting was the most frequent adverse event (5.7%) and the incidence of serious adverse events was 0.2%. All of the serious adverse events occurred in patients who sedated with 70% N_2O/O_2.

2.11 Anxiety and satisfaction assessment

There are many tests that are commonly used to evaluate the level of patient's anxiety such as the Visual Analog Scale (VAS), Dental Anxiety Score (DAS) and State-Trait Anxiety Inventory (STAI). DAS, which was developed by Norman Corah in 1969, is a questionnaire with four questions used to evaluate psychological aspect of patients [56]. STAI is one of the tests that is widely used in psychology research. It

consists of 2 forms and each form contains 20 questions on various situations. STAI is recognized as a gold standard for anxiety evaluation [57].

In contrast to DAS and STAI, VAS is a horizontal line with the length of 100 millimeter. Its two ends are labeled to reflect extreme stage of emotion and patients are required to indicate their degree of feeling such as pain, anxiety or satisfaction by marking on the line. Although DAS and STAI have been widely employed to assess the patient's anxiety, VAS has also been proved to be the successful method to assess wide varieties of subjects' experiences such as pain, mood and anxiety [57-60]. Recently, a Global Anxiety-Visual Analog Scale (GA-VAS) was especially developed for anxiety measurement. Williams et al. [61] had tested the reliability, responsiveness and utility of GA-VAS in patients with General Anxiety Disorder (GAD) and demonstrated that this test was valid and effective for detecting anxiety. VAS has advantages of being simple to use and is largely accepted for its validity and reproducibility [57, 58, 62].

Hennequin et al.[16] investigated the patients' satisfaction on the use of 50% N_2O/O_2 premixed in dentistry and reported that 82% of the patients in their study satisfied with the level of sedation when they were sedated with this premixed product. This information shows the contrast to the original belief that only the slow titration technique would provide satisfaction to the patient.

Nonetheless, there is limited data of the patient's satisfaction on the administrative technique of N_2O/O_2 inhalation sedation. To date, none of studies has ever compared patient's satisfaction between the slow titration and rapid induction techniques of N_2O/O_2 administration.

Regarding its ease of use and wide acceptability, VAS is chosen to be the method for assessing volunteer's anxiety and satisfaction in this study.

2.12 Potential biohazards for health personnel associated with chronic exposure to nitrous oxide

The potential toxicity of N_2O results from its ability to inactivate vitamin B_{12} which plays an important role in many processes in human body such as DNA and catecholamine synthesis. N_2O inhibits methionine synthesis by rapidly oxidize its active co-enzyme, Co(l)alamin, into Co(lll)alamin. The impairment of enzyme remains as long as the N_2O exposure exists. However, after termination of N_2O exposure, this enzyme activity will recover within 3-4 days. In addition, the inhibition of methionine synthesis by nitrous oxide was reported as dose and time dependent [63, 64]. It is believed that N_2O has effects in several body systems including reproductive, neurological, hematological, hepatic and renal systems [29]. Axelsson et al. [65] studied the relation between irregular work time, N_2O exposure and outcome of pregnancy in 1,717 Swedish midwives and reported that nitrous oxide increased risk of spontaneous abortion. Similar to the study of Rowland et al. [66], 50% of pregnant female dental assistants who exposed to unscavenged N_2O five or more hours per week had spontaneous abortion compared to 8% of those unexposed and they also supported that exposure to high level of N_2O without scavenging resulting in the reduction of fertility.

Moreover, N_2O abuse can induce neurologic damage resulting in numbness of the distal extremities, hypoactive reflexes and an electrical shock sensation. Brodsky et al. [67] studied the relationship of N_2O and neurologic diseases by survey in more than

70,000 dentists and chair-side assistants. Their results revealed that the most common neurological symptoms were numbness, tingling and/or muscle weakness. Furthermore, they also reported that dentists who heavily exposed to N_2O, more than 6 hours per week, had complained of symptoms 4 times greater than those who did not expose to N_2O. Nevertheless, the study of Sweeney et al. [68] in 21 volunteer dentists who exposed to N_2O 159-4,000 ppm in 3-11 weeks failed to show neurological abnormalities and their vitamin B_{12} and folate levels were within normal limit. However, morphological abnormalities of bone marrow were seen in 12 of 21 dentists and they concluded that these abnormal changes could result from disturbance of vitamin B_{12} function by N_2O.

From the literature review above, toxicity from nitrous oxide is dose-and time-related then these problems are raised in its chronic exposure. Many investigations have demonstrated that N_2O has gained popularity in its use by dentists [10, 27, 28]. Consequently, the occupational exposure to N_2O is becoming a concern in dental setting. The National Institute for Occupational Safety and Health (NIOSH) has recommended controlling the exposure of N_2O to dental personnel limit of 25 ppm [69] whereas the British Health and Safety Commission established the standard maximal exposure of N_2O to be 100 ppm [70]. Sweeney and colleagues [68] have suggested 400 ppm of nitrous oxide as a safety level without compromising the function of vitamin B_{12}. Yagiela [64] yielded a time-weighted average (TWA) to 100 ppm N_2O 8 hours per day or 400 ppm per anesthetic administration in dental setting that would not affect the biologic effect. Although the recommendations of maximal exposure of N_2O exist, numerous investigators evaluated N_2O in operatory environment and demonstrated that N_2O concentration in many fields were excessive than those

recommendations. Middendorf et al. [71] measured N_2O concentration in 27 dental offices with or without scavenging system. None of the dental offices in their study had N_2O concentration lower than NIOSH's recommendation and maximum N_2O concentration at dentist breathing zones were 132-880 ppm. The study of McGlothlin et al. [72] in pediatric dental clinics with scavenging system reported the mean of N_2O exposure in dentists and their assistants were 438 ppm and 141 ppm, respectively.

The recommendations for controlling N_2O in dental ambience include system maintenance, ventilations and work practice [69]. System maintenance is periodic monitoring and maintenance of N_2O delivery machine to make it functions normally. The connections or deteriorated of rubber goods should be regularly checked to prevent gas leakage, along with monitoring N_2O level in dental operatory. Ventilations comprise of scavenging system, room ventilation, and auxiliary exhausted ventilation [73]. NIOSH recommends the use of scavenging system with maintenance of the exhausted ventilation of N_2O from patient's mask at air flow rate 45 Liter/min [69]. Furthermore, room ventilation should have adequate air flow, 100% clean outdoor air is advised for dental operatory ventilation, and exhausted air vent should be placed at the floor. In addition, auxiliary exhausted ventilation should be placed close to patient's nose in order to remove excess N_2O from breathing zone. For work practice, selection of the appropriate patient also impacts the N_2O in dental environment. Patients who breathe through mouths or exhibit uncooperative behavior such as talking or crying can cause nitrous oxide leakage into ambient air. Moreover, it is prudent to select nasal hood that is appropriate to morphology and size of patient's nose and fits properly. Suitably sedate patient by employing the minimal concentration of N_2O is encouraged [38, 69, 73, 74].