Comparative evaluation of stress levels before, during, and after periodontal surgical procedures with and without nitrous oxide-oxygen inhalation sedation

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INTRODUCTION

Although the pain of periodontal surgical procedures is readily controlled with local anesthesia, the anxiety produced by the dental environment, the discomfort associated with oral injections, and the surgical procedure itself produce varying degrees of stress in all patients.[1] Pain and anxiety, being important stimuli for the secretion of endogenous adrenaline, play a significant role in cardiovascular responses during dental treatment.[2,3] Increased blood pressure, tachycardia, and cardiac arrhythmias have been shown to be a common occurrence during periodontal surgical procedures.[4,5] Severe anxiety can also result in a parasympathetic dominance, which may lead to bradycardia and/or syncope.[6] Respiratory rate is altered during stressful dental procedures, which in time, may alter oxygen saturation and carbon dioxide levels in the blood. Therefore, if psychological stress is controlled, blood gas homeostasis can be well maintained, and medical emergencies in dental office can be avoided.[7] Situations involving pain, anxiety, and acute tissue injury also increase the activity of the hypothalamic–pituitary–adrenal axis which in turn enhances the secretion of cortisol.[8]

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Managing anxiety resulting from dental procedures can be categorized under two main headings:  
- Nonpharmacological: Cognitive behavior therapy, hypnosis, and systemic desensitization  
- Pharmacological: Conscious sedation techniques and general anesthesia.

Conscious sedation has been defined as: “A drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.”[12-14] The options available for conscious sedation are oral, rectal, inhalational, or intravenous sedation. Inhalation sedation is very effective for adult patients with mild-to-moderate anxiety due to dental procedures and needle phobia.[14]

Nitrous oxide-oxygen is the most commonly used inhalation sedative in dentistry.[15-17] It has excellent sedative properties, with little depression of breathing or circulation, and induction and recovery are rapid.[11] It can be utilized for procedures where the efficacy of local anesthesia may be reduced and for potentially more painful procedures, associated with hemodynamic effects, which include alpha-adrenergic effects causing peripheral vasoconstriction and beta-adrenergic effects causing increased cardiac contraction such as periodontal surgical procedures.[3,17]

Stress during periodontal surgical procedures, following administration of intravenous and oral sedation, has been evaluated through serum cortisol levels and vital parameters, namely, blood pressure, pulse rate, and respiratory rate by some investigators.[1,18-20] However, no study was found to evaluate stress levels during periodontal surgery under nitrous oxide-oxygen inhalation sedation. The aim of this study was, therefore, to perform periodontal surgical procedures under nitrous oxide-oxygen inhalation sedation and local anesthesia and assess whether this technique actually reduces stress physiologically, in comparison to local anesthesia alone (LA).

**MATERIALS AND METHODS**

A total of 16 patients (eight males and eight females), aged 30–60 years, requiring periodontal flap surgery in contralateral quadrants, were selected for the study. The sample size was calculated a priori, with an observed power of 99.9%, computed using $\alpha = 0.05$. This study was conducted from May 2013 to September 2014. The plan of the study was submitted to the Research Ethics Committee of the Institute for evaluation, and clearance was granted to carry out this invasive study. This study was carried out in accordance with the Helsinki declaration of 1975, as revised in 2013.

Patients aged between 30 and 60 years, who required periodontal flap surgery in contralateral quadrants and were in the American Society of Anaesthesiologists (ASA) category I or II[21] were enrolled for the study. Patients who showed obstruction to adequate breathing; were drug and substance abusers; had mental disorders; were pregnant; had undergone recent middle ear surgery; in whom gas distention was a problem; were using antidepressants, psychotrophic drugs, and sleep inducing medication; were on bleomycin sulphate therapy; had cystic fibrosis; were mouth breathers; had claustrophobia; were unwilling to accept nasal hood; had upper respiratory tract infections such as common cold, acute or chronic sinus problems, bronchitis, cough; had tuberculosis, sarcoidosis, emphysema, or any other serious respiratory ailment; were smokers; were not willing to undergo nitrous sedation; and were in ASA category III or greater[22] were excluded from the study.

All individuals were informed verbally and in writing about the purpose of the study and were required to sign an informed consent document before participation. Medical and dental history of each patient was recorded. Procedural data were recorded in a specially designed pro forma. A randomized, split-mouth, cross-over study design was used. Two sessions of a similar surgical procedure were performed on each individual by the same operator: one surgical session was performed under local anesthesia aided by nitrous oxide-oxygen inhalation sedation (SS-LAS); and the other SS was performed on the contralateral quadrant under LA on a different day (SS-LA). The selection of the quadrant and the sequence of doing that particular quadrant under nitrous oxide-oxygen inhalation sedation, before the contralateral quadrant without sedation was random. Each surgery was performed at the same time of the day for each patient, and the treatment duration did not affect the study results.

**Blood samples to measure and evaluate serum cortisol levels**

The blood samples were obtained by venipuncture of the antecubital vein, and then centrifuged to separate the serum. The serum samples were frozen and evaluated all at the same time to minimize interassay variation in the assay for serum cortisol. The serum samples were analyzed by fluorometric enzyme immunoassay method, using Cortisol Assay Kit (STAIA Pack CORT kit) with the help of Automatic Enzyme Immunoassay Analyzer (AIA-360 [TOSOH Bioscience]).

**Measurement of vital parameters**

The following vital parameters were monitored for both SSS: blood pressure using a sphygmomanometer, pulse rate with a Finger Pulse Oximeter (Oxxee Check™, Romsons, SN – 113026301212, Model – MD300C26), respiratory rate examined physically, and arterial blood oxygen saturation monitored noninvasively, by a Finger Pulse Oximeter (Oxxee Check™, Romsons, SN – 113026301212, Model – MD300C26).

**Surgical procedure**

The surgical procedure consisted of periodontal flap surgery under (i) LAS SS in one quadrant and (ii) under LA (SS-LA) in the contralateral quadrant of the same patient, performed by the same operator on a different day. It included flap reflection, debridement, osseous recontouring as indicated and closure.

**Surgical session with local anesthesia aided by nitrous oxide-oxygen inhalation sedation**

The continuous flow-type conscious sedation unit (World Wide Sedation, Unicorn DenMart Ltd.) was used to administer nitrous oxide-oxygen inhalation sedation. Nasal hood was
used to administer the gases. In the beginning, 6 L of oxygen was given which corresponded to normal adult tidal volume so as to ensure patient’s ability to breathe comfortably through the hood and to provide required preoxygenation. Then, the concentration of nitrous oxide was increased by an increment of 1 L by rotating the nitrous oxide flowmeter valve counterclockwise, and oxygen was decreased by 1 L by rotating oxygen flowmeter valve clockwise to maintain a total of 6 L. This corresponds to 20% nitrous oxide concentration. Further increase in nitrous oxide was carried out in same way till the patient reported some features of sedation such as light headedness, heaviness, feeling of warmth, tingling in extremities, or slight slurring of speech. A maximum concentration of nitrous oxide used was 67% which means 4 L of nitrous oxide with 2 L of oxygen. Once the patient was sedated, local anesthesia was administered, and the surgical procedure carried out. Following completion of the procedure and on cessation of nitrous oxide administration, nitrous oxide was shut off, and the patient received 100% oxygen for 5 min or longer, if necessary (postsedation oxygenation).

Blood samples were obtained, and the vital parameters were measured and evaluated before sedation (SS-LAS Stage I), 45 min after starting the surgery (SS-LAS Stage II) and once the patient returned to full recovery from sedation (SS-LAS Stage III).

Surgical session with local anesthesia
Surgical sites were anesthetized with local anesthesia. Blood samples were obtained, and vital parameters were measured and evaluated before administration of local anesthesia (SS-LA Stage I), 45 min after starting the surgery (SS-LA Stage II), and after completion of surgery (SS-LA Stage III).

Statistical analysis
The data so collected were put to statistical analysis using statistical package for the social sciences software (SPSS Inc., version 17.0, Manufactured by IBM in March 2015.). Paired t-test and repeated measure ANOVA were applied and results were tabulated.

RESULTS
The present randomized, split-mouth, cross-over study was carried out to compare the stress levels before (Stage I), during (Stage II), and after periodontal surgical procedures (Stage III) with LAS (SS-LAS) and that with LA (SS-LA) on 16 patients (eight males and eight females) requiring periodontal flap surgery in contralateral quadrants. The results have been presented in Tables 1-6.

DISCUSSION
Nitrous oxide is an inhalation agent with anxiolytic and sedative effects combined with varying degrees of analgesia and muscle relaxation. The exact mechanism of action of nitrous oxide is unknown. However, the most widely accepted theory is that the analgesic effect occurs by interaction with the opioid receptors. These are the same receptors activated by morphine and heroin. This stimulation occurs in the midbrain leading to activation of the descending inhibitory pathways, which alters pain processing in the spinal cord. The anxiolytic effect is mediated by interaction with the GABA_A (γ-aminobutyric acid) receptors. The mechanism of action closely resembles that of ethanol. GABA is an inhibitory neurotransmitter that inhibits the presynaptic cells from transmitting thus decreasing nervous system activity.

Serum cortisol levels represented the primary neuroendocrine measure in this study and were significantly lower at 45-min period and upon recovery from sedation than during respective LA experiences (P < 0.001, F = 784.586, S = 0.000). These observations indicate that the patients were more relaxed, and therefore less anxious, when the periodontal surgical procedures were carried out under nitrous oxide-oxygen inhalation sedation, owing to the anxiolytic and analgesic effect of nitrous oxide. The results obtained in this study are in agreement with studies carried out by Hillman et al.\(^1\) and Shepherd et al.\(^3\) who reported significantly lower serum cortisol levels during periodontal surgical procedures, after administration of intravenous sedation, indicating that the patients undergoing periodontal surgery with intravenous conscious sedation experienced reduced stress.

Systolic blood pressure was quite stable in this study after the patients were sedated with nitrous oxide. It was significantly lower at 45-min period and on recovery from sedation than during respective LA experiences (P < 0.001, P = 0.027, respectively, F = 3225.726, S = 0.000). Diastolic blood pressure was also quite stable in this study after the patients were sedated with nitrous oxide and then administered local anesthesia. It was highly significantly lower at 45-min after starting surgery. \(^1\) Sennett et al.\(^2\) reported that there was no significant difference between nitrous oxide-oxygen inhalation sedation and surgical session under local anesthesia alone at different stages.

Table 1: Inter- and intra-session comparison of serum cortisol levels (µg/dl) in surgical session under local anesthesia aided by nitrous oxide-oxygen inhalation sedation and surgical session under local anesthesia alone at different stages

| Surgical session | Mean±SD | Tests of within subjects effects | Stage I versus II | Stage I versus III | Stage II versus III |
|------------------|---------|----------------------------------|------------------|------------------|------------------|
|                  | Stage I | Stage II | Stage III** | F** | S** | Difference | P | Difference | P | Difference | P |
| SS-LAS           | 9.84±2.074 | 7.76±1.899 | 6.57±0.153 | 15.016 | 0.000 | 2.080±1.409 | <0.001 | 3.271±1.242 | <0.001 | 1.91±1.159 | 0.001 |
| SS-LA            | 9.37±2.167 | 10.272±1.984 | 9.307±2.529 | 0.893±0.649 | <0.001 | 0.718±2.37 | 0.005 | 0.965±2.111 | 0.087 |
| Surgical session | Tests of between-subjects effects | Stage I | Stage II | Stage III** |
|                  | F** | S** | Difference | P | Difference | P | Difference | P |
| SS-LAS versus SS-LA | 784.586 | 0.000 | 0.462±0.711 | 0.020 | 2.510±1.372 | <0.001 | 2.737±1.998 | <0.001 |

Paired t-test: *P<0.05 not significant; †P<0.05 significant; ††P<0.001, highly significant; ‡Repeated measure ANOVA. *Stage I – Preoperative; †Stage II – 45 min after starting surgery; **Stage III – Completion of surgery/recovery from sedation. SS-LAS – Surgical session under local anesthesia aided by nitrous oxide-oxygen inhalation sedation; SS-LA – Surgical session under local anesthesia alone; SD – Standard deviation
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Table 2: Inter- and intra-session comparison of systolic blood pressure (mmHg) in surgical session under local anesthesia aided by nitrous oxide-oxygen inhalation sedation and surgical session under local anesthesia alone at different stages

| Surgical session | Mean±SD | Tests of within subjects effects | Stage I versus II | Stage I versus III | Stage II versus III |
|------------------|---------|----------------------------------|-------------------|-------------------|---------------------|
|                  |         |                                  | Difference        | Difference        | Difference          |
|                  |         |                                  | P                 | P                 | P                   |
| SS-LAS           | 125.13±13.446 | 122.50±12.100 122.13±11.581 | 13.123 0.000     | 2.625±1.893 <0.001 | 3.000±3.011 0.001 | 0.375±1.821 0.423 |
| SS-LA            | 123.63±12.05 127.63±11.781 124.13±12.930 | -0.400±1.789 <0.001 | -0.500±1.862 0.300 | 3.500±2.366 <0.001 |

Paired t-test: *P<0.05, not significant; †P<0.05, significant; ‡P<0.01, highly significant; ††Repeated Measure ANOVA. *Stage I – Preoperative; †Stage II – 45 min after starting surgery; ‡Stage III – Completion of surgery/recovery from sedation. SS-LAS – Surgical session under local anesthesia aided by nitrous oxide-oxygen inhalation sedation; SS-LA – Surgical session under local anesthesia alone; SD – Standard deviation.

Table 3: Inter- and intra-session comparison of diastolic blood pressure (mmHg) in surgical session under local anesthesia aided by nitrous oxide-oxygen inhalation sedation and surgical session under local anesthesia alone at different stages

| Surgical session | Mean±SD | Tests of within subjects effects | Stage I versus II | Stage I versus III | Stage II versus III |
|------------------|---------|----------------------------------|-------------------|-------------------|---------------------|
|                  |         |                                  | Difference        | Difference        | Difference          |
|                  |         |                                  | P                 | P                 | P                   |
| SS-LAS           | 80.38±6.820 | 79.00±5.978 78.25±6.234 | 25.918 0.000     | 1.375±1.746 0.007 | 2.125±3.052 0.014 | 750±1.612 0.083 |
| SS-LA            | 79.63±7.05 83.00±7.080 79.00±5.967 | -3.375±0.957 <0.001 | 0.625±1.586 0.136 | 4.000±1.633 <0.001 |

Paired t-test: *P<0.05, not significant; †P<0.05, significant; ‡P<0.01, highly significant; ††Repeated measure ANOVA. *Stage I – Preoperative; †Stage II – 45 min after starting surgery; ‡Stage III – Completion of surgery/recovery from sedation. SS-LAS – Surgical session under local anesthesia aided by nitrous oxide-oxygen inhalation sedation; SS-LA – Surgical session under local anesthesia alone; SD – Standard deviation.

Table 4: Inter- and intra-session comparison of pulse rate (bpm) in surgical session under local anesthesia aided by nitrous oxide-oxygen inhalation sedation and surgical session under local anesthesia alone at different stages

| Surgical session | Mean±SD | Tests of within subjects effects | Stage I versus II | Stage I versus III | Stage II versus III |
|------------------|---------|----------------------------------|-------------------|-------------------|---------------------|
|                  |         |                                  | Difference        | Difference        | Difference          |
|                  |         |                                  | P                 | P                 | P                   |
| SS-LAS           | 73.19±8.085 | 70.50±7.118 69.25±6.537 | 19.819 0.000     | 2.688±2.056 <0.001 | 3.938±3.151 <0.001 | 1.250±1.291 0.002 |
| SS-LA            | 71.38±7.856 | 75.31±7.666 70.44±6.870 | -3.938±1.526 <0.001 | 0.938±3.434 0.401 | 4.875±3.704 <0.001 |

Paired t-test: *P<0.05, not significant; †P<0.05, significant; ‡P<0.01, highly significant; ††Repeated Measure ANOVA. *Stage I – Preoperative; †Stage II – 45 min after starting surgery; ‡Stage III – Completion of surgery/recovery from sedation. SS-LAS – Surgical session under local anesthesia aided by nitrous oxide-oxygen inhalation sedation; SS-LA – Surgical session under local anesthesia alone; SD – Standard deviation.

period than during the respective LA experience (P < 0.001, F = 4666.921, S = 0.000).

In the present study, the lower blood pressure in the SS performed under LAS may have resulted from the anxiolytic effect of nitrous oxide sedation. Nitrous oxide increases venous tone, leading to increased venous return to the heart, and this likely contributes to the stable cardiovascular function observed with nitrous oxide. It was found that the results obtained in this study are in agreement with studies carried out by Hillman et al. and Shepherd et al. who reported a decrease in blood pressure, during periodontal surgical procedures, after administration of intravenous sedation, indicating that the patients undergoing periodontal surgery with intravenous conscious sedation experienced reduced stress.

It has been evaluated that, during the sedation combined with local anesthesia experience, the pulse rate was significantly lower at 45-min period than during the respective LA experience (P < 0.001, F = 3186.869, S = 0.000). This suggests that the stimulus of local anesthetic injections initiated a tachycardic...
response that was partially suppressed by sedation. The above findings are supported by the previous study done by Primosch et al.,[25] who when comparing 100% oxygen inhalation to 40% nitrous oxide supplemented by 60% oxygen inhalation found significant reduction in pulse rate. However, Niwa et al.,[24] found that nitrous oxide sedation had no influence on the cardiovascular response to epinephrine. Nitrous oxide mildly depresses myocardial contractility, but this is offset by its ability to activate sympathetic activity. Therefore, in the present study, the lower pulse rate in the SS performed under LAS may have resulted from the anxiolytic effect of nitrous oxide sedation.

The observations associated with the SS performed under LA can be attributed to the alpha- and beta-adrenergic effect of adrenaline, leading to peripheral vasoconstriction and increased cardiac contraction. Furthermore, the physiological stress of surgery and also painful stimulus following anesthetic injection might lead to increased sympathetic activity and subsequently blood pressure and pulse rate.[3] The results of the present study are consistent with the previous studies by Matsumura et al.[27] and Amoian et al.[3] who reported an increase in blood pressure and pulse rate after anesthesia with lidocaine (2%) and epinephrine (1:80,000).

It has been observed that, during the sedation combined with local anesthesia experience, the arterial blood oxygen saturation was significantly higher at 45-min period than during respective LA experience ($P = 0.002, F = 428182.302, S = 0.000$). The above findings do not agree with a previous study done by Kaviani and Birang,[29] who reported that the mean arterial blood oxygen saturation which before surgery was $98.8\% \pm 0.61\%$, increased to $99.4 \pm 0.17\%$ during surgery under nitrous oxide sedation. The concurrent use of oxygen with nitrous oxide inhalation likely contributed to this finding. The results of the present study are not consistent with the results of a previous study done by Primosch et al.[30] who when comparing 100% oxygen inhalation to 40% nitrous oxide supplemented by 60% oxygen inhalation found significant reduction in respiratory rate but, can be supported by the fact that, nitrous oxide produces a dose-dependent depression of ventilatory drive with a greater influence on the ventilatory response to hypoxemia than to hypercapnia. The increase in respiratory rate produced by nitrous oxide may actually provide a net increase in minute ventilation.[24,28]
sedation, the blood gas homeostasis can be well maintained resulting in increased arterial oxygen saturation.[30]

From the above findings, it seems that the use of nitrous oxide-oxygen inhalation sedation has proven to be an excellent technique to treat periodontal patients and help them overcome their apprehension toward surgical procedures, thereby stabilizing vital parameters and reducing stress levels. It is inexpensive and has an impeccable safety record, with several advantages over other modalities of conscious sedation.

CONCLUSION

Nitrous oxide-oxygen inhalation sedation for periodontal surgical procedures is capable of reducing stress physiologically, in comparison to local anesthesia alone during lengthy periodontal surgical procedures.

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Conflicts of interest
There are no conflicts of interest.

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